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LEVEL OF VITAMIN A IN THE BLOOD AS AN INDEX OF VITAMIN A DEFICIENCY IN INFANTS AND IN CHILDREN

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In previous communications [1] we have reported on the vitamin A requirements of infants and of children. The criteria which we used for estimating the vitamin A status of the subjects were (1) growth, (2) susceptibility to infections and (3) visual threshold in the dark (dark adaptation). The results of the studies indicated that, as judged by the aforementioned criteria, the requirement for vitamin A is low and that the average diet of infants and children contains several times the minimum requirement. It is for this reason that patients with frank vitamin A deficiency are so uncommonly observed in the clinic.

The possibility exists, however, that states of subclinical vitamin A deficiency are much more prevalent. In view of the fact that the level of vitamin C in the blood is now regarded as an indicator of the size of the stores of vitamin C in the body and is of considerable value in the diagnosis of subclinical vitamin C deficiency, the question was raised as to whether the same situation obtains in regard to vitamin A.

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1. (*a*) Barenberg, L. H., and Lewis, J. M.: Relationship of Vitamin A to Respiratory Infections in Infants, J. A. M. A. **98**:199 (Jan. 16) 1932. (*b*) Hess, A. F.; Lewis, J. M., and Barenberg, L. H.: Does Our Dietary Require Vitamin A Supplement? **101**:657 (Aug. 26) 1933. (*c*) Lewis, J. M., and Barenberg, L. H.: Relationship of Vitamin A to the Health of Infants, ibid. **110**:1338 (April 23) 1938. (*d*) Lewis, J. M., and Haig, C.: Vitamin A Requirements in Infancy as Determined by Dark Adaptation, J. Pediat. **15**:812, 1939. (*e*) Lewis, J. M., and Haig, C.: Vitamin A Status of Children as Determined by Dark Adaptation, ibid. **16**:285, 1940.

Recent reports [2] have indicated that the vitamin A content of the blood can be measured accurately by a modification of the Price-Carr procedure. The present study was undertaken to determine, in infants and in children, the relation of the concentration of vitamin A in the blood to the intake of the vitamin and to dark adaptation. We hoped thereby to obtain information which might be of aid in evaluating the use of the level of vitamin A in the blood as an indicator of vitamin A deficiency.

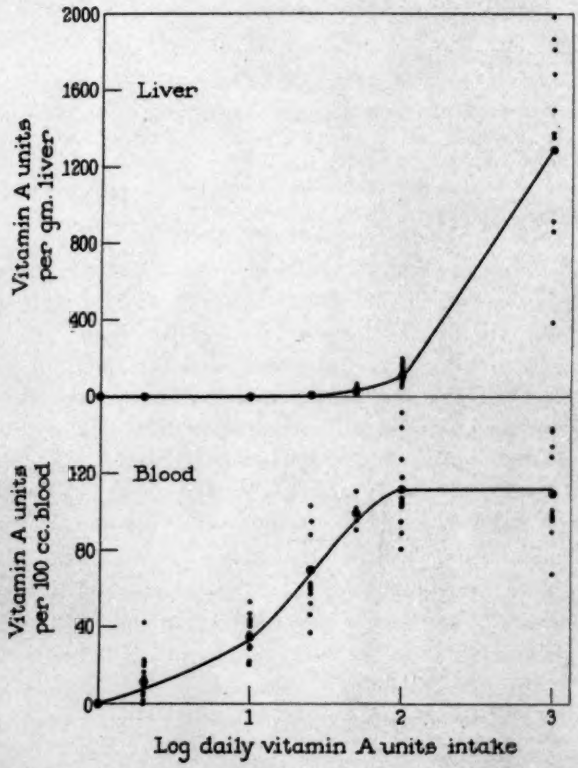

Chart 1.—Relation of the intake of vitamin A to the level of the vitamin in the blood and to its storage in the liver in rats.

Preliminary experiments concerning the relation of the level of vitamin A in the blood to the intake of the vitamin and to its storage in the liver were carried out on rats. The results of these experiments,

2. (*a*) Clausen, S. W., and McCoord, A. B.: The Carotinoids and Blood Vitamin A, J. Pediat. **13**:635, 1938. (*b*) Kimble, M. S.: Vitamin A and Carotene in Human Plasma, J. Lab. & Clin. Med. **24**:1055, 1939. (*c*) May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allan, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 (June) 1940.

which were reported in another communication,[3] are illustrated in chart 1. It will be observed that the concentration of vitamin A in the blood was directly related to the intake when the amount of vitamin A fed was less than 50 U. S. P. units daily. Increasing the feeding to 100 and to 1,000 units daily had no appreciable effect on the level of the vitamin in the blood but resulted in the storage of larger amounts of the vitamin in the liver. With regard to the relation of the level of vitamin A in the blood to its storage in the liver, it will be observed that concentrations of less than 35 U. S. P. units per hundred cubic centimeters of plasma were associated with no vitamin A in the liver, and those between 35 and 50 units were accompanied by little or no storage, whereas levels above 50 units were always associated with vitamin A in the liver, the amount stored varying considerably and having no relation to the absolute level of the vitamin in the blood.

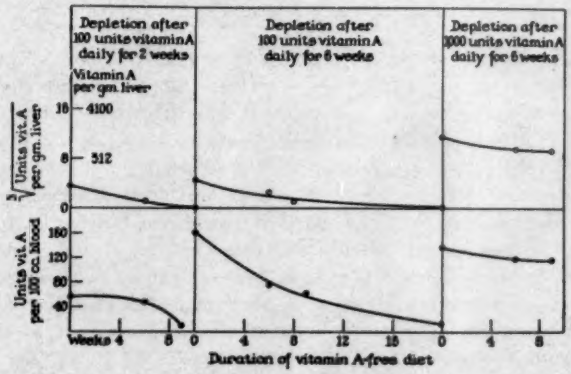

Chart 2.—Effect of a diet devoid of vitamin A on the level of the vitamin in the blood and its storage in the liver in rats previously fed varying amounts of vitamin A.

The effect of a vitamin A–free diet on the level of vitamin A in the blood and on the reserve in the liver in rats previously fed varying amounts of vitamin A was also investigated. The results of this study are shown in chart 2. It will be seen that when the stores of vitamin A in the liver were large the concentration of the vitamin in the blood was maintained at a high level over a period of nine weeks, despite the consumption of a diet devoid of vitamin A. On the other hand, when the stores in the liver were low they became rapidly depleted and during the time they were being exhausted the concentration of the vitamin A in the blood fell, reaching low levels when the liver no longer contained vitamin A. Thus, the depletion experiments also revealed that low concentrations of vitamin A in the blood were associated with an

3. Lewis, J. M.; Bodansky, O.; Falk, K. G., and McGuire, G.: Relationship of Vitamin A Blood Level in the Rat to Vitamin A Intake and to Liver Storage, Proc. Soc. Exper. Biol. & Med. **46**:248, 1941.

absence of storage of vitamin A in the liver. The experiments in rats, therefore, indicated that the level in the blood may be of value in ascertaining whether there is any storage of vitamin A in the liver, the chief reservoir of this vitamin in the body.

STUDIES ON INFANTS

After having established the relation of the intake of vitamin A to its level in the blood and to its storage in the liver in rats, we began our investigations on infants. One hundred and forty-four infants were placed on diets containing varying amounts of vitamin A and the relation of the intake of vitamin A to its level in the blood [4] and to dark adaptation [5] was determined. One group of infants received an average diet; a second group, an average diet supplemented with large quantities of vitamin A in the form of halbiut liver oil; a third group, a diet low in vitamin A, that is, containing about one-fourth the vitamin A content of

4. The method employed for determination of the vitamin A content of the blood was based on the Price-Carr reaction. Since the carotenoids also give a blue reaction with antimony trichloride, it was necessary to determine the carotene content of the blood. The vitamin A and carotene in the blood were extracted with purified petroleum benzine U. S. P. (petroleum ether), as recommended by Clausen and McCoord. To 3 to 5 cc. of blood plasma 5 cc. of 95 per cent ethyl alcohol and 8 cc. of purified petroleum benzine were added. The mixture was shaken for ten minutes and then centrifuged. Six cubic centimeters of the supernatant purified petroleum benzine extract was measured for its carotene content as 440 micromicrons with an Evelyn photoelectric colorimeter. The number of micrograms of carotene was determined by means of a calibration curve obtained with a sample of pure carotene supplied to us by the General Biochemicals Company, Cleveland. The purified petroleum benzine was evaporated in a water bath at 70 C., a stream of nitrogen being passed through the liquid during evaporation. The oily residue was dissolved in 0.6 cc. of chloroform, and 5.4 cc. of a 25 per cent solution of antimony trichloride (in chloroform) was added. The intensity of the resulting blue color was measured at 620 micromicrons in the Evelyn photoelectric colorimeter. The reading was translated into biologic (U. S. P.) units, by referring to a calibration curve obtained with a sample of halibut liver oil of known biologic potency. The vitamin A content of the plasma was calculated after subtracting the value for carotene.

5. The procedure and the instrument employed for carrying out the dark adaptation test on infants have been fully described in a previous communication (Haig, C., and Lewis, J. M.: Simple Method of Measuring Brightness Threshold of Dark Adapted Eye at All Ages, Proc. Soc. Exper. Biol. & Med. **41**:415, 1939). Briefly, the procedure is as follows. The infant is placed in a dark room for thirty minutes to allow the eyes to become fully adapted to the dark. Then a light of known intensity is moved from side to side through an arc of 180 degrees at a distance of approximately 10 cm. from the baby's eyes. The minimum intensity of light which elicits a movement of the head (indicated by a movement of a luminous vial attached to the forehead) in the direction of the light is considered the infant's threshold for vision in the dark. This threshold represents the final rod threshold, which has been shown by a number of investigators to be high in cases of vitamin A deficiency.

the average diet, and a fourth group, a diet devoid of vitamin A. These infants were harbored in an institution for child care [6] and were therefore under close observation. Infants are usually admitted to this institution when they are less than 3 months of age, and a complete history with respect to previous administration of preparations containing vitamin A was obtained. Those infants who had received supplements of vitamin A prior to admission were placed in the group receiving the diet high in vitamin A.

Table 1 shows a comparison of the levels of vitamin A in the blood of 64 infants receiving an average diet [7] and of 62 receiving an average diet supplemented daily with 14 drops of halibut liver oil,[8] which supplied approximately 17,000 U. S. P. units of vitamin A, for periods varying from one to five months. Specimens of blood for vitamin A

TABLE 1.—*Comparison of the Levels of Vitamin A in the Blood of Infants Receiving an Average Diet and of Those Receiving an Average Diet Supplemented with Vitamin A in the Form of Halibut Liver Oil* *

Age, Months	Number of Infants Receiving		Average Level of Vitamin A in Blood Plasma, Units per 100 Cc. for Infants Receiving		Range of Levels of Vitamin A in Blood Plasma, Units per 100 Cc. for Infants Receiving	
	Average Diet	Average Diet and Halibut Liver Oil	Average Diet	Average Diet and Halibut Liver Oil	Average Diet	Average Diet and Halibut Liver Oil
¾ - 3	35	25	71	93	45-106	50-151
3 - 6	11	22	78	93	56-114	50-160
6 - 12	13	9	110	112	67-141	85-141
12 - 18	5	6	110	100	90-118	81-116

* The halibut liver oil was given for periods varying from one to five months, and the daily dose was 17,000 U. S. P. units.

analysis were taken forty-eight hours after the last administration of the concentrate in order to make sure that the concentration of vitamin A was at a postabsorptive level.

During the first six months of life the addition of this large amount of vitamin A to the average diet brought about an increase in the vitamin A content of the blood. Thus, the average level of vitamin A in the blood of infants 3 weeks to 6 months of age who received the average diet was 74 units per hundred cubic centimeters of plasma, whereas those receiving the diet high in vitamin A had an average con-

6. Home for Hebrew Infants.

7. The diet in the institution may be regarded as an average diet. For example, 1 to 2 ounces (30 to 60 cc.) of milk was given per pound (453 Gm.) of body weight, the amount depending on the age of the infant; orange juice was prescribed at 6 weeks, cereal at 4 months, vegetables at 6 months, desserts at 8 months, eggs at 10 months and meat at 1 year of age.

8. The halibut liver oil was supplied by Mead Johnson & Co.

centration of 93 units.[9] On the other hand, supplementing the diet with 17,000 units of vitamin A had no effect on the level of vitamin A in the blood of infants 6 to 18 months of age, the vitamin A concentration being 110 units for those receiving the average diet and 107 units for those receiving the diet high in vitamin A. Maximal concentrations of vitamin A in the blood were thus attained with the unsupplemented average diet in infants over 6 months of age. It should be added that there was no difference in the vitamin A content of the blood of male and of female infants.

The diet employed in the institution for infants over 6 months of age contains considerably more vitamin A (chiefly because of the addition of vegetables) than the diet for younger infants, and it is probable that the higher concentrations of vitamin A in the blood noted for the older infants was due not to the age factor but rather to the greater intake of the vitamin. In this connection it may be added that we have recently observed a normal well nourished infant 8 months of age who received no vegetables in the diet and had a level of 54 units of vitamin A per hundred cubic centimeters of blood plasma, a value which we have generally observed for infants less than 6 months of age.

The lowest concentrations of vitamin A in the blood obtained for the infants from 3 weeks to 6 months of age, 46 of whom received the average diet and 47 the diet high in vitamin A, were 45 and 50 units respectively per hundred cubic centimeters. It therefore seems that values below 45 units might be regarded as subnormal for infants of this age group.

The results of the dark adaptation tests for infants receiving an average diet and for those receiving a diet supplemented with vitamin A were reported in a previous communication.[1d] It was found that there was no difference between the visual thresholds (after complete dark adaptation) for the two groups of infants.

The effect on the level of vitamin A in the blood and on dark adaptation of a diet providing only about 335 units of vitamin A[10] daily (approximately one-fourth the vitamin A content of the average diet for infants under 6 months of age) was studied in 6 infants, who were 3 weeks to 2½ months of age. This diet consisted of partly skimmed milk (containing 0.8 per cent fat), ascorbic acid (25 mg.), viosterol

9. The difference between 74 units, the mean value for the group of infants receiving the average diet, and 93 units, the mean value for those receiving halibut liver oil, was more than three times the standard error of the difference (4.7). The chances that a true difference exists between the values for the two groups are at least 999 in 1,000.

10. Dornbush and his co-workers have reported recently (Dornbush, A. C.; Peterman, W. H., and Olsen, F. R.: The Carotene and Vitamin A Content of Market Milks, J. A. M. A. **114**:1748 [May 4] 1940) that a quart (946 cc.) of market milk (containing 3.5 per cent fat) contains an average of 1,460 units of vitamin A. Since the vitamin is present in the butter fat only, a quart of milk having a fat content of 0.8 per cent contains about 335 units of vitamin A.

in oil (10 drops) and a white wheat cereal (farina); it was given for periods varying from two to four months. In table 2 may be noted the effect of the diet low in vitamin A on the concentration of the vitamin in the blood and on dark adaptation. It will be seen that the average concentration in the blood fell from 74 to 61 units per hundred cubic centimeters. However, in no instance did the concentration of vitamin A fall to an abnormally low level, that is, below 45 units. It may also be noted that the dark adaptation of all 6 infants remained normal.

The level of vitamin A in the blood and the ability of the eye to adapt to darkness were determined for 12 infants who received a diet devoid of vitamin A. These infants ranged in age from 1½ to 4 months. The diet consisted of ascorbic acid (25 mg.), viosterol in oil (10 drops), a white wheat cereal (farina) and a special preparation of milk, the butter

TABLE 2.—*Effect of a Diet Low in Vitamin A on the Concentration of Vitamin A in the Blood and on Dark Adaptation* *

Subject	Age When Diet Was Begun, Months	Duration of Diet, Months	Level of Vitamin A in Blood Plasma, Units per 100 Cc.		Dark Adaptation at End of Administration of Diet
			Prior to Institution of Diet	At End of Administration of Diet	
C. K.	¾	2	69	49	Normal
R. G.	1½	2½	76	68	Normal
B. Z.	2½	4	80	58	Normal
C. P.	2	4	80	75	Normal
P. C.	1	4	80	57	Normal
T. B.	¾	4	60	56	Normal
Average			74	61	

* The daily diet contained approximately 335 U. S. P. units of vitamin A.

fat of which was replaced by a vegetable oil. The infants received this vitamin A–free diet for periods varying from two weeks to four and one-half months.

In table 3 one may observe the results of the consumption of the vitamin A–free diet on the concentration of vitamin A in the blood and on dark adaptation. When the diet was given for periods of two to six weeks 1 of 4 infants showed an abnormally low concentration of the vitamin (37 units) in the blood. On the other hand, when the diet was given for two to four and a half months the concentration of vitamin A in the blood of 6 of 8 infants became abnormally low, reaching levels as low as 11 units per hundred cubic centimeters of plasma. It may also be noted that the 2 infants (R. S. and S. G.) in whose blood concentration of the vitamin did not fall to subnormal levels had received 17,000 units of vitamin A daily for one month prior to the institution of the vitamin A–free diet. It is probable that these infants had accumulated large stores of vitamin A in their livers during the administration of the vitamin A concentrate and that these depots maintained the concentra-

tion of the vitamin in the blood at a high level despite the administration of a diet devoid of the vitamin.

Poor dark adaptation was noted for all 7 infants who manifested low levels of vitamin A in the blood. It should be emphasized that these

TABLE 3.—*Effect of a Diet Devoid of Vitamin A on the Concentration of Vitamin A in the Blood and on Dark Adaptation*

Subject	Age When Diet Was Begun Months	Duration of Diet, Months	Level of Vitamin A in Blood Plasma, Units per 100 Cc.		Dark Adaptation at End of Administration of Diet
			Prior to Institution of Diet	At End of Administration of Diet	
E. G.	6	0	93	..	Normal
H. R.	4½	0	62	..	Normal
A. R.	2¾	½	52	57	Normal
J. B.	4	1	103	37	Abnormal
S. K.	1¼	1	85	51	Borderline
A. C.	1½	1½	90	87	.....
A. I.	1½	2	93	44	Abnormal
J. K.	1½	2	..	13	Abnormal
L. R.	1¾	2	52	30	Abnormal
N. R.	3½	2	54	11	Abnormal
R. S.*	3	2⅓	96	76	.....
R. B.	3½	3⅓	103	29	Abnormal
S. G.*	4	4	113	54	Borderline
J. R.	1½	4½	84	23	Abnormal

* This infant had received 14 drops of halibut liver oil (supplying 17,000 U. S. P. units of vitamin A) daily for one month prior to the administration of the vitamin A-free diet.

TABLE 4.—*Concentration of Vitamin A in the Blood of Patients with Diseases Affecting the Absorption of Fat*

Patient	Age, Years	Level of Vitamin A in Blood Plasma, Units per 100 Cc.	Abnormal Condition
K. A.	1/12	27	Steatorrhea; prematurity
B. G.*	1/3	16	Cystic fibrosis of the pancreas
L. R.	1/2	7	Congenital obstruction of the bile ducts
T. F.	1	39	Celiac disease
M. D.	2	2	Congenital obstruction of the bile ducts
R. G.	2	30	Celiac disease
A. C.	6	35	Catarrhal jaundice
L. P.*	Adult	0	Carcinoma of the pancreas

* An assay of the vitamin A content of the liver of this patient was carried out post mortem and revealed a very low value, that is, 3 units per gram.

infants appeared normal in every way; they had gained weight well and had been no more susceptible to infections than the infants receiving large quantities of vitamin A in the diet. They may therefore be regarded as having subclinical vitamin A deficiency, which was made evident only by the dark adaptation test and the analysis of the blood for vitamin A.

In table 4 are recorded the values for the concentration of vitamin A in the blood for 6 infants, 1 child and 1 adult who had disorders which

affect the absorption of fat, namely, congenital obliteration of the bile ducts, cystic fibrosis of the pancreas, celiac disease, catarrhal jaundice, steatorrhea of the premature infant and, finally, in the adult, carcinoma of the pancreas. The values were low for all 8 patients, an observation in agreement with the results of other investigators.[2a] Dark adaptation tests were carried out on the infant, aged 4 months, who had cystic fibrosis of the pancreas and on the adult, who had carcinoma of the pancreas, and in both instances abnormally high thresholds were discovered. These 2 patients died, and their livers were analyzed for vitamin A. The results of the analysis in both instances revealed very low amounts, 3 units of vitamin A per gram of liver as compared with the average values of 130 units for normal 4 month old infants [11] and 290 units for adults.[12]

During the neonatal period the values for the concentration of vitamin A in the blood may be low and yet may not necessarily indicate

TABLE 5.—*Values for the Concentration of Vitamin A in the Blood During the Neonatal Period*

Age, Days	Total Number of Infants	Distribution of Infants on the Basis of Units of Vitamin A per 100 Cc. of Plasma						
		20-29	30-39	40-49	50-59	60-69	70-89	90-139
At birth	24	0	0	2	9	5	4	4
1 - 2	23	3	11	1	3	3	1	1
3 - 4	9	1	3	0	1	2	1	1
5 - 6	11	0	1	2	2	2	2	2
7 -10	10	1	2	1	2	3	1	0

the presence of low stores of the vitamin in the body. In table 5 the values for the concentration of vitamin A in the blood of 77 newborn infants are reported. It will be observed that at birth none of 24 infants had a value lower than 40 units per hundred cubic centimeters. On the other hand, during the first four days of life there was a sharp drop in the level of vitamin A in the blood, the concentration for 18 of 32 infants reaching levels between 20 and 39 units. During the latter part of the neonatal period the concentration of vitamin A in the blood reached normal levels in most instances. The fall in the levels during the first few days of life is probably due not only to a low intake of vitamin A during this period but to a failure of the liver to mobilize

11. Ellison, J. B., and Moore, T.: Vitamin A and Carotene: The Vitamin A Reserve of Human Infant and Child in Health and Disease, Biochem. J. **31**:165, 1937.

12. Moore, T.: Vitamin A and Carotene: The Vitamin A Reserve of the Adult Human Being in Health and Disease, Biochem. J. **31**:155, 1937.

vitamin A into the blood, since we have found that the livers of most newborn infants which we have assayed contain considerable quantities of vitamin A. In table 6 are listed the results of analyzing for vitamin A the livers of 20 newborn infants. It will be seen that the average total number of units of vitamin A per liver was 12,655 and that the average number of units per gram of liver was 115. These values are much higher than those previously reported by Wolff,[13] who examined the livers of newborn babies in Holland and found an average of 42 international units per gram of liver.

TABLE 6.—*Vitamin A Content of the Liver of Twenty Newborn Infants*

Case No.	Total Units of Vitamin A in Liver	Units of Vitamin A per Gram of Liver	Comment
1*	40	1	Premature (6 mo.) stillborn infant
2	150	3	Full term stillborn infant; mother had obstructive jaundice for 3 weeks prior to delivery
3	1,160	16	Premature (8½ mo.) infant; lived 15 hr.
4	2,620	23	Premature (7½ mo.) infant; lived 27 hr.
5*	5,240	38	Full term stillborn infant
6	5,200	40	Premature (8 mo.) infant; lived 1 day
7*	7,420	53	Full term infant; lived 3 days
8	5,200	55	Full term stillborn infant
9	8,680	56	Premature (5 mo.) stillborn infant
10	2,295	62	Premature (5½ mo.) stillborn infant
11	6,470	66	Full term infant; lived 13 hr.
12	7,200	72	Full term stillborn infant
13	9,550	104	Premature (7½ mo.) infant; lived 1 hr.
14	13,000	104	Premature (8½ mo.) stillborn infant
15*	4,840	121	Premature (7½ mo.) infant; lived 2 hr.
16	10,020	167	Premature (8½ mo.) stillborn infant
17	20,400	204	Full term infant; lived 4 days
18	36,600	282	Full term stillborn infant
19	61,380	341	Full term infant; lived 6 hr.
20*	45,650	507	Premature (8 mo.) stillborn infant
Average	12,655	115	

* The liver of this infant was not weighed; the total vitamin A content was calculated on the basis of expected weight.

Comment.—The study therefore revealed that low levels of vitamin A in the blood occurred when infants received diets devoid of vitamin A or had disorders which brought about an interference with the absorption of fat. The low level of vitamin A in the blood was found to be associated with poor dark adaptation and also with low storage of the vitamin in the liver. The observations on infants are, therefore, in agreement with the results of our experiments on rats and show that low levels of vitamin A in the blood indicate the presence of vitamin A deficiency.

13. Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, Lancet **2**:617, 1932.

The increase in the level of vitamin A in the blood during the first six months of life as a result of the administration of vitamin A concentrates raises the question of whether preparations containing vitamin A should be administered routinely to infants of this age group. The fact that the levels for older infants and for children are normally higher than those for younger infants may indicate that higher levels are more desirable physiologically, although at present no evidence to this effect exists. In this connection it is of interest to add that when rats with high levels of vitamin A in the blood as a result of the administration of large quantities of the vitamin were placed on diets devoid of vitamin A the concentrations in the blood continued to remain high at the expense of the vitamin A reserve in the liver. Although no data are available indicating that infants with high levels of vitamin A in the blood are in a better state of health than those with "normal" levels, it is known that the administration of vitamin A supplements results in larger stores in the body. Such reserves would be of value to those infants in whom there develops one of the disorders which may bring about a low intake of the vitamin or may interfere with its absorption. From the foregoing considerations it seems advisable to administer preparations containing vitamin A routinely during the early months of life.

STUDIES ON OLDER CHILDREN

Determinations of the level of vitamin A in the blood and dark adaptation tests were carried out on 157 children, 6 to 12 years of age, who were patients in the wards of the children's medical division of Bellevue Hospital. These children were divided into the following three groups.

1. The normal group consisted of 19 children who either were boarders in the wards of the hospital or had been admitted for a minor cutaneous ailment, for example, scabies or ringworm.

2. The afebrile, or miscellaneous, group consisted of 118 children who had been admitted to the hospital because of the following disorders: infection of the upper respiratory tract, rheumatic fever, dysentery, asthma, renal calculus, glomerulonephritis, erysipelas, sickle cell anemia and Hodgkin's disease. Determinations of the vitamin A content of the blood and dark adaptation tests were carried out on the children of this group only when the temperature was normal.

3. The febrile group consisted of 20 children who had fever when the concentration of vitamin A in the blood and the visual threshold in the dark were determined.

In chart 3 the distribution of the levels of vitamin A in the blood for the three groups of children is illustrated. The normal group had

the highest values, the afebrile had intermediate levels and the febrile had the lowest concentrations of vitamin A in the blood. As may be noted in table 7, the average value for the concentration of vitamin A in the blood was 117 units per hundred cubic centimeters for the normal group, 89 units for the afebrile group and 44 units for the febrile group. The sharp drop in the concentration of vitamin A in the blood during fever has been demonstrated previously by Clausen and McCoord.[2a]

It may be noted that the average level of vitamin A in the blood for 19 normal children [14] 6 to 12 years of age is about the same as that obtained for normal infants 6 to 18 months of age (table 1), being

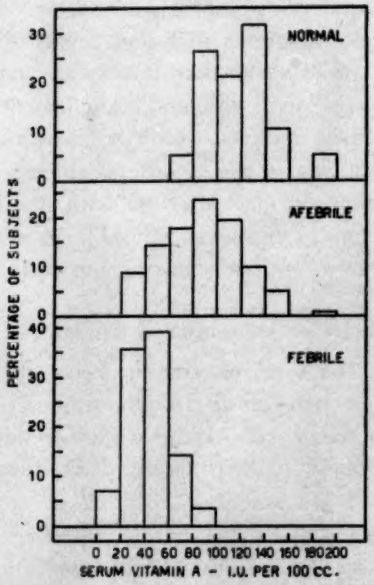

Chart 3.—Percentage distribution of the values for the concentration of vitamin A in the blood for three groups of children.

117 units for the former as compared with 110 units for the latter. The lowest concentration of vitamin A was 70 units for the children and 67 units for the infants. It therefore appears that values lower than 67 units may be regarded as subnormal for children between the ages of 6 months and 12 years.

14. We have recently made determinations of the vitamin A content of the blood of normal adults, and our results are in agreement with those reported by Kimble, namely, an average of 127 U. S. P. units per hundred cubic centimeters of plasma for males and 91 units for females.

In the febrile group 17 of the 20 children had values below 67 units. Such low values are transitory, the concentration of vitamin A in the blood usually returning to normal within a few days after the disappearance of fever. In the afebrile, or miscellaneous, group 22, or 19 per cent, of the 118 children had subnormal levels of the vitamin in the blood. Examinations were carried out on some of these children within twenty-four to forty-eight hours after the temperature returned to normal, and it is possible that the incidence of diminished values for the concentration of vitamin A in the blood in the afebrile group might have been lower if the values had been obtained later in the afebrile period.

The results of dark adaptation tests for the three groups of children may be noted in chart 4. In a previous communication [1e] we showed that the minimum intensity of light visible to normal children when their eyes were fully dark adapted varied from 1.6 to 2.5.[15] A threshold greater than 2.5 is regarded as abnormally high and indicates the pres-

TABLE 7.—*Level of Vitamin A in the Blood and Dark Adaptation of Children Six to Twelve Years of Age*

Group	Number of Children	Level of Vitamin A in Blood Plasma, Units per 100 Cc.		Number of Children with Abnormal Dark Adaptation
		Average	Range	
Normal	19	117	70-197	0
Afebrile	118	89	25-198	1
Febrile	20	44	10- 95	4

ence of vitamin A deficiency, provided, of course, that there is no organic lesion in the eye to account for the poor dark adaptation.

In chart 4 it may be observed that none of the normal children in this study manifested high thresholds in the dark. The incidence of abnormal thresholds was low in the afebrile group, only 1 (0.9 per cent) of the 118 children showing poor dark adaptation. On the other hand, the incidence of abnormal visual thresholds in the dark was high in the febrile group, 4 (20 per cent) of the 20 children showing poor dark adaptation. As may be noted in table 8, the visual threshold of 2 of the febrile children (L. C. and L. L.) became normal as soon as the fever disappeared. The threshold of 1 child (M. R.) remained high for many weeks despite the return of the temperature to normal and the administration of 200,000 units of vitamin A daily.

This low incidence of poor dark adaptation among the afebrile children is in agreement with the results of our previous study, in which

15. "The photometric unit employed was the micromicrolambert (1 micromicrolambert = 1 foot candle $\times$ 1.076 $\times$ 10^{-9}), and, for simplicity, the threshold values obtained were expressed in terms of logarithmic units."[1d]

we found an abnormally high threshold for only 1 of 144 children. In their most recent paper on the prevalence of vitamin A deficiency in children as judged by dark adaptation Jeans [16] and his co-workers reported that of 180 children in an orphanage who were tested with the biophotometer none was observed to have subnormal dark adaptation. These investigators found that of 120 school children examined during the winter only 5 had thresholds in the subnormal range; 50 of these children were retested late in the spring, and in no instance was the threshold in the subnormal range. Hecht and Mandelbaum [17] have

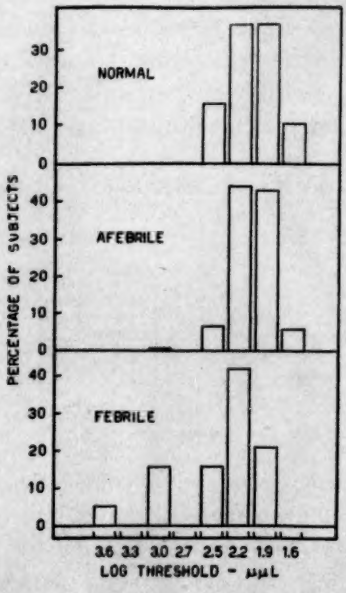

Chart 4.—Percentage distribution of the values for minimum light thresholds, obtained by dark adaptation tests, for the three groups of children. Thresholds higher than 2.5 are abnormal.

found a low incidence of poor dark adaptation also among adults, only 1 of 106 showing an abnormal threshold.

In chart 5 the relation of the level of vitamin A in the blood to the visual threshold is illustrated. Five children had abnormal thresholds (3.0 to 3.6), and for 4 of these 5 the concentration of vitamin A in the blood was less than 40 units per hundred cubic centimeters. Within the

16. Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A, J. Pediat. **18**:170, 1941.

17. Hecht, S., and Mandelbaum, J.: The Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1910 (May 13) 1939.

normal range of blood levels (67 to 198 units) there was no correlation between the vitamin A content of the blood and the ability of the eye to adapt to the dark. However, when the levels of vitamin A in the

TABLE 8.—*Level of Vitamin A in the Blood and Dark Adaptation of Children with Febrile Diseases*

Patient	Age, Years	Level of Vitamin A in Blood Plasma, Units per 100 Cc.	Dark Adaptation	Disease	Comment
E. A.	12	10	Abnormal	Tuberculous peritonitis	Temperature 103 to 104 F. for several weeks
L. L.	12	18	Abnormal	Rheumatic fever	Temperature 104 to 105 F. for 5 days; with return of temperature to normal level of vitamin A in blood rose rapidly to 113 units and dark adaptation became normal
M. B.	12	24	Normal	Pneumonia	Temperature 104 to 105 F. for 2 days
M. R.	12	32	Abnormal	Rheumatic fever	Temperature 102.5 F. for 3 days; with return of temperature to normal level of vitamin A in blood rose to 133 units but dark adaptation remained abnormal for several weeks despite administration of large quantities of vitamin A (200,000 units daily)
T. T.	11	32	Normal	Pneumonia	Temperature 103 to 104 F. for 3 days
R. S.	5	33	Normal	Rheumatoid arthritis	Temperature 100 to 103 F. for several weeks
L. C.	11	35	Abnormal	Pulmonary tuberculosis	Temperature 103 to 104 F. for several weeks; with return of temperature to normal, level of vitamin A in blood rose rapidly to 90 units and dark adaptation became normal
S. S.	10	37	Normal	Rheumatic fever	Temperature 100 to 102 F. for several weeks; assay of liver post mortem revealed 270 units of vitamin A per gram, a normal value
R. E.	11	42	Normal	Acute tonsillitis	Temperature 102 to 103 F. for 1 week
P. R.	3	43	Normal	Acute nasopharyngitis	Temperature 102 to 103 F. for several days
W. W.	6	44	Normal	Undiagnosed	Temperature 101 to 102 F. for 3 weeks
E. P.	6	48	Normal	Acute tonsillitis	Temperature 103 F. for 6 days
A. G.	12	52	Normal	Acute bronchitis	Temperature 103 F. for 5 days
F. E.	6	53	Normal	Subacute bacterial endocarditis	Temperature 100 to 101 F. for several weeks
D. F.	9½	55	Normal	Acute nasopharyngitis	Temperature 102 F. for 1 week
M. M.	7	59	Normal	Postscarlatinal arthritis	Temperature 101 to 102 F. for several days
E. P.	6	61	Normal	Acute bronchitis	Temperature 102 F. for several days
A. M.	8	67	Normal	Acute nasopharyngitis	Temperature 101.5 F. for 1 week
A. K.	7	70	Normal	Rheumatic fever	Temperature 100 to 101 F. for 3 weeks
B. G.	7	95	Normal	Rheumatic fever	Temperature 100.5 F. for 3 weeks

blood were very low (less than 40 units), the visual threshold for 4 of 15 children was abnormally high. It may be noted that for all of 22 afebrile children who had concentrations of vitamin A lower than 67 units per hundred cubic centimeters of blood dark adaptation was normal. It is possible that the low levels of vitamin A in this group

were transitory especially in the case of the children who had recently recovered from a febrile illness. At any rate these observations suggest that the level of vitamin A in the blood is a more delicate indicator of vitamin A deficiency than is the result of the dark adaptation test.[18] It should be added, however, that 1 child had an abnormally high visual threshold in the dark and yet had a normal level of vitamin A, 79 units per hundred cubic centimeters of plasma. Administration of large quantities of vitamin A, totaling 200,000 units, brought about a return of the threshold to normal in forty minutes. This exceptional child may have had a high requirement for vitamin A or may have had a disturbance in the utilization of the vitamin in the retina. This experience indicates that the dark adaptation test should not be discarded in favor of determination of the level of vitamin A in the blood. For the

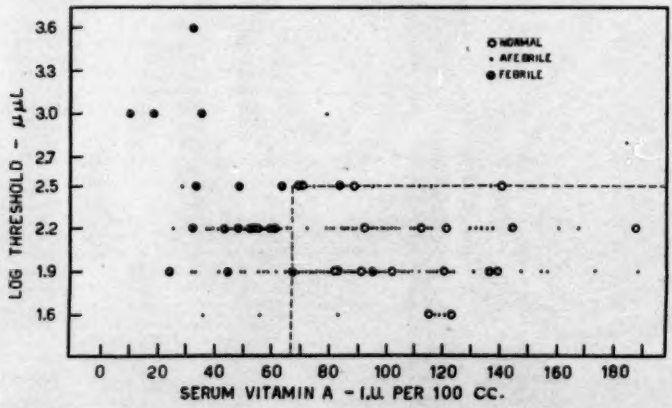

Chart 5.—Relation of the level of vitamin A in the blood to the minimum light threshold of the three groups of children. The horizontal line, at the level of 2.5, indicates the upper limit of the normal threshold range obtained for fully dark-adapted children, and the vertical line, at 67 units, indicates the lower limit of the normal range of levels of vitamin A in the blood for children.

complete evaluation of the vitamin A status both procedures should be employed.

The high incidence of vitamin A deficiency among patients with febrile disorders merits consideration. That such patients' low levels of vitamin A in the blood do not necessarily indicate low stores of the vitamin in the body may be seen from the following example. A 10 year

18. In this connection it is of interest that Haig and Patek (Haig, C., and Patek, A. J., Jr.: [supp.] Anat. Rec., to be published) have recently found that for patients with cirrhosis of the liver the level of vitamin A in the blood is a more sensitive index of vitamin A deficiency than is the result of the dark adaptation test.

old boy with rheumatic fever had had a temperature of 100 to 102 F. for many weeks. Several days before his death the concentration of vitamin A in his blood was 37 units per hundred cubic centimeters, a definitely low value. Analysis of his liver for vitamin A revealed a value of 270 U. S. P. units per gram, as compared with the average of 130 units for a normal child of his age. The foregoing experience suggests that in febrile diseases there may be an interference with the mobilization of vitamin A from the liver into the blood. The resultant low levels in the blood may lead to poor dark adaptation, a manifestation of vitamin A deficiency.

This raises the question of whether it is advisable to administer vitamin A concentrates to patients with febrile diseases, especially to those with diseases of a chronic nature. To obtain information on the

TABLE 9.—*Effect of the Administration of Vitamin A Concentrates on the Level of Vitamin A in the Blood of Children with Febrile Diseases*

Patient	Age, Years	Units of Vitamin A Administered Daily	Duration of Vitamin A Therapy, Days	Level of Vitamin A in Blood Plasma, Units per 100 Cc.		Disease
				Prior to Therapy	After Therapy	
F. M.	½	25,000	2	47	71	Nasopharyngitis
A. P.	¾	25,000	2	25	53	Pneumonia
G. W.	¾	25,000	2	42	80	Adenitis
B. M.	1	25,000	2	20	84	Pneumonia
H. E.	6	120,000	1	67	153	Subacute bacterial endocarditis
J. K.	6	17,000	2	37	100	Adenitis
D. V.	6	17,000	2	51	49	Gangrenous appendicitis
L. K.	8	120,000	1	38	72	Rheumatic fever
Average				41	83	

effect of vitamin A concentrates on the level of the vitamin in the blood in febrile diseases we gave large quantities of vitamin A, 17,000 to 120,000 units, to 8 children ranging in age from 6 months to 8 years. The blood was examined before the administration of vitamin A and twenty-four hours after the dose was given. As may be observed in table 9, there was a rise in the level of the vitamin in the blood of 7 of the 8 children, and in 6 instances the vitamin A content became normal in twenty-four to forty-eight hours. The average level of vitamin A in the blood for the 8 children was 41 units prior to the administration of the vitamin and 83 units after it was given. These observations offer a rationale for the use of vitamin A preparations in treating patients with febrile disorders, especially those which are likely to be of long duration.

SUMMARY AND CONCLUSIONS

Low levels of vitamin A in the blood in rats were found to be associated with low intakes of the vitamin and with little or no storage in the liver.

The lowest level of vitamin A in the blood observed in examinations of 144 normal infants was 45 U.S.P. units per hundred cubic centimeters. Values below this level were obtained for infants receiving diets devoid of vitamin A and for those suffering from disorders which affected the absorption of fat. A low level of vitamin A in the blood was associated with poor dark adaptation and with low storage of the vitamin in the liver. The observations on infants are therefore in agreement with the results of the experiments on rats and show that low levels of vitamin A in the blood indicate the presence of vitamin A deficiency.

The daily administration of 17,000 units of vitamin A to infants during their first six months of life brought about an increase in the vitamin A content of the blood. On the other hand, no appreciable effect on the level of vitamin A in the blood was noted when infants between the ages of 6 and 18 months were given the vitamin A preparation daily for periods varying from one to five months. In view of these observations, it would seem advisable to give vitamin A concentrate routinely to infants during the early months of life.

The incidence of poor dark adaptation was low among afebrile children, only 1 of 118 manifesting an abnormally high visual threshold in the dark. On the other hand, 4 of 20 children examined during the course of a febrile illness were found to have poor dark adaptation. The importance of febrile disorders in the development of vitamin A deficiency is therefore apparent.

The level of vitamin A in the blood was low during febrile diseases, but with the administration of vitamin A concentrates a rise in the level was noted for 6 of 8 patients in twenty-four to forty-eight hours. It therefore seems advisable to administer preparations containing vitamin A to patients with febrile illnesses which are likely to be of long duration.

Of 118 afebrile children, 22 were found to have low concentrations of vitamin A in the blood associated with normal dark adaptation. This observation suggests that the level of vitamin A in the blood may be a more sensitive indicator of vitamin A deficiency than is the result of the dark adaptation test. However, one may occasionally observe normal level of the vitamin in the blood in the presence of abnormal dark adaptation. We are therefore of the opinion that to investigate fully the vitamin A status the dark adaptation test, as well as a determination of the level of vitamin A in the blood, should be carried out whenever possible.

ABSTRACT OF DISCUSSION

DR. ARTHUR F. ABT (Chicago): When Dr. Lewis asked me to discuss this paper he suggested that I comment on some of the similarities between the results of studies on vitamin C and of those on vitamin A. My associates and I reported

in 1935 that the level of ascorbic acid in the blood varies directly with the intake of vitamin C. Dr. Lewis and his co-workers have shown that this also holds for vitamin A. Our purpose in 1935 was to develop a method by which to discover the early stages of vitamin C subnutrition. Dr. Lewis has indicated that subnormal values for the level of the vitamin in the blood are also an early indication of vitamin A subnutrition. We did not try, as some observers have thought we did, to develop a chemical test for scurvy, for we believe that any physician who deals with diseases of children can diagnose scurvy by means of the clinical signs and symptoms. We investigated and abandoned methods using determinations on whole blood; our work has been carried out on blood plasma.

Values for the levels of vitamins A and C in the plasma are more delicate indicators than the results of examinations on the whole blood, the determination of the storage of the vitamins in the body or the results of dark adaptation tests for detecting subclinical vitamin A and vitamin C deficiencies. We may also state that subnutrition with respect to a single vitamin may indicate that there is an accompanying multiple avitaminosis.

High fasting values for the concentration of ascorbic acid in the plasma mean an adequate intake of vitamin C. A single low value for the concentration of ascorbic acid in the plasma may mean (*a*) an inadequate intake of vitamin C or (*b*) an adequate intake but a failure of absorption, an infection or the antagonistic action of a heavy metal. Fever is not a factor. We have studied the effect of fever per se, in the absence of infection and have found that it does not lower the concentration of vitamin C in the plasma. As we showed last spring, certain heavy metals have an antagonistic action on the level of vitamin C in the plasma. If iron and vitamin C are given at the same time the hemoglobin content will rise and the concentration of vitamin C in the plasma will fall. Administration of arsenic and vitamin C has the same effect.

A single low value, that is one between 0.4 and 0 mg. per hundred cubic centimeters, need not mean scurvy. Saturation by oral or intravenous administration of the vitamin will show this; repeated single determinations may indicate latent or subclinical avitaminosis. Dr. Lewis' preceptor, Dr. Alfred Hess, of New York, was the first to suggest the concept of latent, or subclinical, avitaminosis.

A patient with scurvy, especially an infant, will not necessarily have a zero level of vitamin C in the plasma. There is marked individual variation.

In studying the patients, most of whom were adults, at the Municipal Social Hygiene Clinic in Chicago, we found that when the diet was poor the values for the concentration of vitamin A in the plasma were low, when the vitamin A content of the diet was fair the values were higher and when the vitamin A content of the diet was good the values were increased. This is in accord with the observations Dr. Lewis and his associates have made on infants.

We observed a pregnant woman who was 92 pounds (41.7 Kg.) overweight. However, she was overweight not because of a high intake of fat but because her diet was high in starch. She was given ascorbic acid and cod liver oil and arsenic treatment for syphilis. The level of vitamin A in her plasma rose, but there was a great drop in the level of vitamin C, because of the administration of arsenic.

An underweight patient with a high value for vitamin A (125 units per hundred cubic centimeters of plasma) had been taking cod liver oil. When the cod liver oil was discontinued the value dropped. For a group of male patients the average value for vitamin A was 102 units, for a group of females 92 units and for a group

of pregnant women, only 72 units, which indicates that the pregnant woman should be given vitamin A. It is imperative to pay attention to the vitamin A intake of the pregnant woman.

DR. J. M. LEWIS, New York: Dr. Abt mentioned that febrile disorders brought about a lowering of the level of vitamin C in the blood as well as a reduction in the vitamin C stores in the body. The level of vitamin A in the blood is also decreased by febrile diseases, and, as was shown by Clausen, it is the high temperature rather than the associated toxemia which is responsible. Thus, it was found that when the temperature was elevated by artificial fever treatments the level of vitamin A in the blood fell rapidly. It should be emphasized that the low levels of vitamin A in the blood associated with acute febrile disorders are transitory and do not necessarily mean low stores of vitamin A in the body.

Dr. Abt stated that he found low values for vitamin A in the blood for pregnant women. We have had the same experience, and the routine administration of vitamin A concentrates to pregnant women, as he suggested, seems well indicated.

PHYSICAL AND CHEMICAL PROPERTIES OF SPUTUM

II. INFLUENCE OF DRUGS, STEAM, CARBON DIOXIDE AND OXYGEN

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AND

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In the first part of this study spontaneous variations in the physical and chemical qualities of sputum were observed and summarized and their relation to mechanical drainage was discussed.[1] The mechanical drainage of the secretions of the bronchi is accomplished by the action of the cilia, the respiratory movements, the tussive squeeze of the cough reflex, the cough itself and, finally, expectoration. That these processes, both the cellular and the more gross mechanical ones, may be aided by the use of expectorants is well recognized.[2] The most commonly used means of increasing endobronchial drainage at present consist of the administration of expectorants, which cause a more active bronchial secretion or liquefy the sputum and make it less tenacious.

The specific influence on the sputum of commonly used expectorants, such as drugs and steam, is knowledge which has been obtained through centuries of clinical experience. In most instances the efficiency of the expectorants has been judged by clinical examination of the chest and measurement of the total amount of sputum raised. More recently, such observations have been augmented by the results of experimental studies. Connell, Johnston and Boyd[3] obtained pharmacologic evidence of the influence of expectorants by weighing the respiratory tracts of laboratory

This work was supported by a grant from the Theodore B. Sachs Residency Fund.

From the Department of Pediatrics and the Department of Otology, Rhinology and Laryngology (Bronchoesophagology), University of Illinois College of Medicine.

1. Basch, F. P.; Holinger, P., and Poncher, H. G.: Physical and Chemical Properties of Sputum: I. Factors Determining Variations in Portions from Different Parts of the Tracheobronchial Tree, Am. J. Dis. Child. **62**:981 (Nov.) 1941.

2. Basch, F. P.: Die Behandlung der Bronchiektasien im Kindesalter, Wien. klin. Wchnschr. **43**:361-62 (March 20) 1930.

3. Connell, W. F.; Johnston, G. M., and Boyd, E. M.: On Expectorant Action of Resyl and Other Guaiacols, Canad. M. A. J. **42**:220-223 (March) 1940.

animals of equal weights after the injection of an expectorant. The trachea, the alveolar part and the bronchial part of the tract were weighed separately after the administration of guaiacol, guaiacol carbonate and glyceroguaiacol ether in syrup (resyl). They found that only the water content of the trachea increased and that there were no histologic changes.

Gordonoff [4] emphasized another property of expectorants, that of increasing the natural resorption ability of the alveolar tissue. It is generally recognized that the lungs are able to resorb liquids in the form of water and exudates and solids, such as dust. This faculty has been termed "self cleaning of the alveoli." Gordonoff demonstrated this mechanism by injecting an isotonic sugar solution into the lungs of experimental animals; the blood sugar level reached its maximum after thirty minutes and dropped to normal after one hundred and twenty minutes. He found that the administration of an expectorant at the same time (potassium iodide or saponins) caused a much higher resorption of the injected sugar. The maximum level of the blood sugar became higher, and the normal level was reached much later.

Gordonoff further emphasized the importance of the rate of respiration as a factor in increasing the upward movement of the secretion in the bronchial tree. He found that a more rapid movement of secretions followed an increase in the respiratory rate. The use of ammonium chloride, in his opinion, was effective not only through its local action but also because of the generalized acidosis it produced. The p_H of the blood dropped during the administration of this drug from 7.6 to 7.5, and consequently the respiratory volume increased from 6 to 10 and, occasionally, to 15 liters per minute. This observation led us to use inhalations of carbon dioxide, in order to see whether the hyperventilation so produced had any influence on expectoration.

The use of inhalations of carbon dioxide for resuscitation in many types of respiratory accidents need not be described. Such inhalations have been found to have other therapeutic applications as well. Campbell and Poulton [5] observed definite improvement in a patient with severe asthma after the administration of oxygen and carbon dioxide, while the same patient failed to improve with administration of oxygen alone. Their observations are as follows:

During the sixteen hours spent in a tent with 40 per cent oxygen and 2 to 4 per cent carbon dioxide the patient had a productive cough and raised sputum freely. During five hours in an atmosphere of 40 to

4. Gordonoff, T.: Physiologie und Pharmakologie des Expektorationsvorganges, Ergebn. d. Physiol. **40**:53-100, 1938.

5. Campbell, A., and Poulton, E. P.: Oxygen and Carbon Dioxide Therapy, ed. 2, London, Oxford University Press, 1938, pp. 78-79.

50 per cent oxygen and no carbon dioxide the patient obtained no relief. Greatest improvement in the cough followed a period of six hours during which 20 to 25 per cent oxygen and 2.5 to 4 per cent carbon dioxide were administered. These same authors found that the use of oxygen alone did not seem to prevent attacks of asthma, but the administration of carbon dioxide with oxygen did seem to have an effect, and they expressed the belief that the use of such administrations would be advisable in cases of refractory asthma in order to break the sequence of attacks. Care must be exercised, however, for some patients were found to be intolerant of such therapy.

Another of their observations concerned the effect of carbon dioxide on a young woman with extensive pneumonia who was given inhalations of oxygen through a closed circuit apparatus. The carbon dioxide absorption container was too small, so that carbon dioxide accumulated in an hour or two and the patient was panting excessively before the apparatus was removed. To the physician's surprise, the patient showed marked clinical improvement.

This phenomenon was studied experimentally in artificially induced pneumonia in a dog; the carbon dioxide again produced coughing, and the animal expectorated. This was followed by a rapid clearing of the lung.

Alison [6] used inhalations of 5 per cent carbon dioxide with oxygen in some cases of beginning pneumonia and bronchitis, especially in children. He expressed the belief that the disease process was aborted through the removal of the mechanical blocking of the airways.

Campbell and Poulton interpreted the action of carbon dioxide in pneumonia as threefold:

1. In a concentration of 4 to 5 per cent it induces cough and helps to dislodge plugs of mucus.

2. When a plug which has produced atelectasis is removed, the latter clears up more rapidly with administration of carbon dioxide than without (experimental observations).

3. It may act by modifying the p_H of the exudate, decreasing its viscosity and causing proteolysis, since the pneumococcus is very sensitive to an acid medium.

Further observations on the expectorant action of carbon dioxide have been recorded by Banyai,[7] who used inhalations of 10 per cent carbon dioxide in oxygen in cases of pulmonary tuberculosis. He observed that the increase in respiratory rate was followed by easier

6. Alison, J. F.: Carbon Dioxide in the Treatment of Acute Bronchitis and Early Pneumonia, South. M. J. **25**:386-389 (April) 1932.

7. Banyai, A. L.: Carbon Dioxide Inhalation in Pulmonary Tuberculosis, Am. Rev. Tuberc. **30**:642-652 (Dec.) 1934.

expectoration and decrease of cough. By means of almost effortless expectoration large amounts of sputum were evacuated. The sputum changed from a heavy, thick and tenacious type to a thinner, serous and more watery form.

MATERIALS AND METHODS

The sputum of patients with bronchiectasis was used in these studies; it was collected both by carefully observed postural drainage and by bronchoscopic suction. This sputum was used for the studies because, as was indicated previously, the normal secretions of the tracheobronchial tree are not, in the usual sense, sputum, for when such physiologic exudates become copious enough to be expectorated a pathologic condition exists.

In the present studies, several hundred examinations of sputum were made to determine the p_H, viscosity, amount of dried residue and percentage of ash. The total nitrogen and the chloride content were determined by the methods described previously.

Studies regarding the influence of expectorants on the total quantity of expectorated material were made in earlier portions of this investigation. Observations were made on 2 patients for seventy-one and twenty-one days, and the proportions of pus, mucus and saliva (the usual three divisions) with and without treatment were determined. This study revealed that the amount of sputum obtained is not a justifiable index of the action of an expectorant or antiexpectorant. The use of chewing gum, variations in rest periods and activity and daily differences in the temperature and humidity of the room all greatly influence the total daily amount of sputum even of untreated patients; these factors also influence the actual collection of the total sputum.

Test periods, during which medication was administered, lasted several days in each case. Patients were observed during control periods, during which they received no medication, for from two to seven days prior to the test periods in order to determine the qualities of the sputum when the patient was untreated. The average results for the test period were taken as representative of that experiment, the entirely abnormal results which occasionally occurred being neglected.

The p_H and the total nitrogen content of the sputum proved of minor importance; consequently, these properties were not determined in the advanced stage of the work. The value of the chloride content of the sputum proved to be irregular, and many samples contained no chlorides. It became necessary to consider this part of the examination as a special problem which would require a separate investigation.

The drugs were given at regular intervals day and night in the usual dosage, which was determined by the age of the patient. Only emetine hydrochloride and atropine sulfate were administered subcutaneously.

Tests to note the influence of an increase in humidity were made, two types of humidifiers being employed. In the first experiment steam inhalators were used, the patient inhaling the vapor three times a day for half-hour periods. In the second test mechanical humidifiers which produced a high degree of humidity by the mechanical vaporization of cold water were used.

Gas (carbon dioxide, oxygen and mixtures of the two) was administered through a rubber tube, directly from the tank. The mouth and nose of the patient were covered by a mask, the eyes remaining free. Special care was taken to make certain that the nozzle of the tube was located in the mask above the nostrils, in order to prevent any irritation of the nasal mucosa by the gas, especially that

which might be caused by carbon dioxide. The amount of the inhaled gas was measured by a flow meter. Carbon dioxide was given repeatedly during the day for periods of five to ten minutes in an amount just sufficient to produce marked hyperventilation without causing dizziness or headache. It was necessary to change this method for the test periods prior to bronchoscopic examinations. In such instances, the gases were administered throughout the hour before the examination.

Oxygen was administered from a tank by the direct method, the tube passing to a mask covering the nose and mouth. In those cases in which oxygen was to be administered for a longer period, an intranasal catheter was used. This method differs from the other in that the oxygen passes through a water bottle, which increases its moisture content.

TABLE 1.—*Influence of Ammonuim Chloride on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
N. C.	None	..	8.1	4.5	0.7	16.1	7.5	0.4	3.1	0.15
	Ammonium chloride	..	7.8	6.8	0.9	12.8	7.6	0.5	1.4	0.09
A. S.	None	20	...	7.1	0.7	9.8	11.6	0.8		
	Ammonium chloride	9	...	7.5	0.7	10.0	11.3	0.8		
V. W.	None	..	8.0	10.0	1.0	10.4	11.0	1.16	2.4	0.24
	Ammonium chloride	..	7.9	9.0	0.9	9.1	18.5	1.70	0	0
	None	..	...	8.7	1.0	11.3	17.7	1.54	0	0
V. W.	None	..	...	4.8	0.7	14.7	7.7	0.36		
	Ammonium chloride	..	...	7.4	0.8	11.1	11.0	0.82		
V. W.	None	32	...	6.1	0.9	14.6	9.0	0.55		
	Ammonium chloride	23	...	8.0	0.7	9.0	12.0	0.96		

* Thirty-four examinations were made.

RESULTS

Ammonium Chloride (34 examinations).—The viscosity and the p_H of the sputum were lowered and its dried residue was increased. The amount of ash and the output of chlorides were influenced only insignificantly. The total nitrogen content of the sputum was regularly and markedly higher after treatment with ammonium chloride (table 1).

Potassium Iodide (21 examinations).—The viscosity and the p_H were lowered. In the sputum of 1 patient (11 examinations) the dried residue, the amount of ash and the total nitrogen content were increased; in that of another (10 examinations) the dried residue was slightly lowered, the amount of ash remained unchanged and the total nitrogen content was markedly lowered (table 2).

Fluidextract of Senega (58 examinations).—The viscosity was markedly reduced, but the p_H was not influenced. The dried residue

of the sputum was increased in the majority of the cases during its administration; the amount of ash was not appreciably changed, and the total nitrogen content was increased (table 3).

TABLE 2.—*Influence of Potassium Iodide on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
N. C.	None	..	8.1	4.5	0.7	16.1	7.5	0.4	3.1	0.15
	Potassium Iodide	..	7.9	7.3	0.9	11.8	8.4	0.7	1.3	0.09
N. W.	None	34-46	...	6.5	0.8	11.3	10.3	0.65		
	Potassium Iodide	24	...	6.2	0.8	12.4	7.1	0.43		

* Twenty-one examinations were made.

TABLE 3.—*Influence of Fluidextract on Senega* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
N. C.	None	..	8.1	4.5	0.7	16.1	7.5	0.4	3.1	0.15
	Fluidextract of senega	..	8.0-8.2	8.0	0.9	11.2	9.6	0.8		
	None	..	8.0	6.4	0.8	13.6	7.1	0.5	1.7	0.10
V. W.	None	90	...	7.3	1.1	15.0	13.4	0.97		
	Fluidextract of senega	23	...	7.7	0.8	11.4	10.1	0.77		
V. W.	None	17	...	8.1	0.8	9.4	10.1	0.91		
	Fluidextract of senega	14	...	7.9	0.8	9.7	11.5	0.90		
V. W.	None	70	...	10.0	0.8	8.5				
	Fluidextract of senega	36	...	8.7	0.9	10.1				
	Fluidextract of senega	14	...	6.8	0.8	11.0				
	Fluidextract of senega	24								
	Fluidextract of senega	24								
R. B.	None	2	...	6.3	0.8	12.7				
	Fluidextract of senega	1	...	6.3	0.9	13.4				
	Fluidextract of senega	2	...	7.2	0.8	10.7				
	Fluidextract of senega	2	...	7.1	0.8	12.1				

* Fifty-eight examinations were made.

Fluidextract of Ipecac (28 examinations).—The viscosity of the sputum was lowered, but its p_H was not influenced. The dried residue of the sputum of 2 patients increased markedly (19 examinations); that of the sputum of another patient was reduced (9 examinations). The

amount of ash increased slightly; the total nitrogen content increased in the sputum of 1 patient, who had 14 examinations, and was found to be lower in that of another, who had 4 examinations (table 4).

Emetine Hydrochloride (50 examinations).—The effect of this drug was studied before the sputum was tested routinely with the viscosim-

TABLE 4.—*Influence of Fluidextract of Ipecac on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
N. O.	None	..	8.0	6.4	0.8	13.6	7.1	0.5	1.7	0.10
	Fluidextract of ipecac	..	8.0	8.9	0.9	10.4	11.6	1.04	0.7	0.07
V. W.	None	..	...	7.8	0.7	8.9	14.9	1.15	1.7	0.21
	Fluidextract of ipecac	..	8.0	6.3	0.7	11.6	10.3	0.66		
	Fluidextract of ipecac	..	8.0	7.8	0.8	10.2	7.5	0.57	3.4	0.26
V. W.	None	35	...	6.3	0.8	13.8				
	Fluidextract of ipecac	21	...	5.2	0.8	13.9				
R. B.	None	8	...	5.7	0.8	14.3				
	Fluidextract of ipecac	6	...	6.2	0.8	12.2				
	Fluidextract of ipecac	4	...	6.0	0.8	13.8				
	Fluidextract of ipecac	6	...	6.0	0.9	14.1				

* Twenty-eight examinations were made.

TABLE 5.—*Influence of Emetine Hydrochloride on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
N. O.	None	..	8.0	6.4	0.8	13.6	7.1	0.50	1.7	0.10
	Emetine hydrochloride	..	8.1	8.1	0.9	10.8	11.2	0.88	0	0
	None	..	...	6.3	0.8	13.1	7.5	0.45	0.7	0.05
V. W.	None	..	8.0	8.0	0.8	10.2	9.1	0.76	0.7	0.05
	Emetine hydrochloride	..	8.1	7.4	0.8	10.8	7.5	0.56	0	0
	None	..	7.8	7.1	0.7	10.1	7.7	0.57	0.92	0.07
	Emetine hydrochloride	..	8.0	8.2	0.8	10.0	10.4	0.86	0.9	0.07

* Fifty examinations were made.

eter, and consequently its influence on viscosity was not determined. The p_H of the sputum was increased slightly, the dried residue was irregularly influenced and the amount of ash was not influenced by its use. The total nitrogen content was increased fairly constantly (table 5).

Inhalations of Steam or Moisture (30 examinations).—The viscosity was greatly lowered; the influence on the p_H was irregular. The dried

TABLE 6.—*Influence of Inhalations of Steam or Moisture on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash: Dried Residue, %	Ash: Total Sputum, %	Total Nitrogen Content: Dried Residue, %	Total Nitrogen Content: Total Sputum, %	Chloride Content: Dried Residue, %	Chloride Content: Total Sputum, %
N. C.	None	..	8.1	4.5	0.7	16.1	7.5	0.4	3.1	0.15
	Inhalations of steam	..	7.8-8.6	3.3	0.8	23.0	3.2	0.1	2.8	0.09
V. W.	None	..	8.0	8.0	0.8	10.2	9.1	0.76	0.7	0.05
	Inhalations of steam	..	8.0	5.9	0.8	14.8	6.7	0.43	0.7	0.05
V. W.	None	..	...	8.7	1.0	11.3	17.7	1.54		
	Inhalations of steam	..	7.9	7.5	0.7	9.3	10.1	0.77		
V. W.	None	40	...	8.0	0.8	10.1	14.4	1.14		
	Inhalations of steam	24	...	6.3	0.8	12.1	14.3	0.91		
V. W.	None	32	...	6.1	0.9	14.6	9.0	0.55		
	Inhalations of steam	19	...	7.3	0.8	11.5	11.6	0.84		
V. W.	None	33	...	7.6	0.8	10.8				
	Inhalations of moisture	17	...	5.8	0.8	14.3				

* Thirty examinations were made.

TABLE 7.—*Influence of Inhalations of Carbon Dioxide on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash: Dried Residue, %	Ash: Total Sputum, %	Total Nitrogen Content: Dried Residue, %	Total Nitrogen Content: Total Sputum, %	Chloride Content: Dried Residue, %	Chloride Content: Total Sputum, %
V. W.	None	..	8.0	9.6	0.8	8.3	16.0	1.54	1.42	0.15
	Inhalations of carbon dioxide	..	7.8	7.8	0.8	10.0	12.8	1.30	0	0
V. W.	None	..	7.9	8.6	0.8	10.0				
	Inhalations of carbon dioxide	..	...	7.1	0.5	7.5				
V. W.	None	34	...	8.7	0.9	8.6				
	Inhalations of carbon dioxide	19	...	7.8	0.8	10.4				
V. W.	None	8	...	5.7	0.8	14.3				
	Inhalations of carbon dioxide	3	...	6.2	0.8	12.2				
V. W.	None	600	...	9.4	0.9	10.0				
	Inhalations of carbon dioxide	30	...	7.8	0.9	11.4				
	Inhalations of carbon dioxide	40	...	8.9	0.9	10.6				

* Sixteen examinations were made.

residue and the total nitrogen content were usually markedly lowered, while the amount of ash was slightly lowered (table 6).

Inhalations of Carbon Dioxide (52 examinations).—The viscosity and the dried residue were regularly and markedly lowered. The amount of ash and the total nitrogen content were irregularly lowered (table 7).

Results of Bronchoscopic Examinations After Inhalations of Carbon Dioxide: There were definite changes in the character of the mucosa after inhalations of carbon dioxide. The mucous membrane appeared more reddened and velvety than it had on previous examinations, and the walls had a tendency to ooze more easily on contact with the bronchoscope or aspirator. There was a definite suggestion of congestion

TABLE 8.—*Influence of Inhalations of Carbon Dioxide on the Mucosa and Secretions of the Tracheobronchial Tree* *

Patient	Mucous Membrane	Sputum in Tracheobronchial Tree	
		Quantity	Quality
M. T.	Injected		
	Thickened		
	Pale, thickened	Very small	Tenacious
	Reddened	.....	Thickened, tenacious
	Injected	Very small	
J. W.	.....	Decreased	More liquid than in most cases
		Decreased	
		Small	
L. D.	.....	Decreased	More liquid
		Small	More liquid
		No secretion	
	Pale	Small	Less viscous
A. W.	Unchanged	Copious	Very liquid
	Unchanged	Copious	Very liquid
	Unchanged	Copious	Thinner
	Unchanged	Copious	Liquid but somewhat gelatinous
E. M.	Red	Moderate	Very liquid; foul
	Red	Less	Less copious
	Normal	Scanty	

* Nineteen examinations were made.

of the mucosa. Changes in the consistency of the sputum were likewise noted. After such administrations the amount of sputum was markedly decreased in every case, but in spite of this it appeared to have become thinner. A foamy character was noted after all inhalations of the gas. Exceptions to these changes were found in cases in which the secretion was copious, probably because the gas could not satisfactorily diffuse throughout the lung.

It should be noted that the irritation of the mucous membrane, as evidenced by redness, was observed only in the parts of the airways in which pathologic conditions were present. The mucous membrane of the nose, the mouth and the larynx was unchanged (table 8).

Combination of Expectorant Drugs and Inhalations of Steam (18 examinations).—Table 9 shows the effects of a combination of inhala-

tions of steam with administration of fluidextract of ipecac or ammonium chloride. The viscosity was lowered by using either steam or one of the drugs alone, but it was lowered considerably more if they were given together (additive effect). The dried residue was increased by administration of the drugs and lowered after the use of steam. The amount of ash was influenced very slightly; the total nitrogen content was increased by use of the drugs alone and reduced by the dilution of the secretion after inhalation of steam.

TABLE 9.—*Influence on Sputum of a Combination of Drugs and Inhalations of Steam* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
V. W.	None	..	8.1	7.8	0.7	8.9	14.9	1.15	1.7	0.21
	Steam and fluidextract of ipecac	..	...	5.7	0.8	13.9	7.9	0.45	1.2	0.07
V. W.	Fluidextract of ipecac	..	8.0	7.8	0.8	12.2	7.5	0.57	3.4	0.26
	Steam and fluidextract of ipecac	..	...	5.3	0.8	15.5				
	Steam and fluidextract of ipecac	..	...	4.6	0.9	17.9	6.4	0.30	2.7	0.66
	None	..	8.4	5.5	0.8	14.7	5.9	0.32	1.05	0.06
V. W.	Steam and emetine hydrochloride	11	8.4	5.2	0.8	17.0	6.8	0.27		
	Emetine hydrochloride	14	...	4.9	0.8	15.9	7.4	0.37		
V. W.	None	32	...	6.1	0.9	14.6				
	Steam	19	...	7.3	0.8	11.5				
	Ammonium chloride	23	...	8.0	0.7	9.0				
	Steam and ammonium chloride	14	...	6.5	0.9	14.2				
	None	33	...	7.6	0.8	10.8				

* Eighteen examinations were made.

Inhalations of Carbon Dioxide and Steam (15 examinations).—There was a remarkable lowering of the viscosity. The p_H was increased, and the dried residue and the total nitrogen content were reduced markedly and the amount of ash to a lesser degree (table 10).

Combination of Expectorant Drugs and Inhalations of Carbon Dioxide and Steam (12 examinations).—This combination caused the most marked lowering of the viscosity of the sputum achieved in this experimental study. The p_H was increased. The influence on the dried residue was found to be different for the 2 patients examined. The amount of ash was not appreciably influenced (table 11).

TABLE 10.—*Influence on Sputum of a Combination of Inhalations of Carbon Dioxide and Steam* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
V. W.	None	..	...	8.7	1.0	11.3	17.7	1.54	0
	Steam	..	7.9	7.5	0.7	9.3	10.1	0.77	1.06
	Steam and carbon dioxide	..	8.1	8.0	0.8	9.8	8.8	0.70	1.38
V. W.	None	..	7.9	8.6	0.8	10.0	15.2	1.3	1.4
	Steam and carbon dioxide	..	8.2	6.0	1.0	16.2	6.7	0.4	1.36
V. W.	None	40	...	8.0	0.8	10.1	14.4	1.14	
	Steam	24	8.0	6.3	0.8	12.1	14.3	0.91	
	Steam and carbon dioxide	4	...	5.4	0.7	13.0	10.7	0.59	
	None	32	...	6.1	0.9	14.6	9.0	0.55	

* Fifteen examinations were made.

TABLE 11.—*Influence on Sputum of a Combination of Expectorant Drugs and Inhalations of Carbon Dioxide and Steam* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
V. W.	Fluidextract of ipecac	..	8.0	6.3	0.7	11.6	10.3	0.66	
	Fluidextract of ipecac and carbon dioxide	..	...	5.7	0.6	10.9	11.5	0.66	
V. W.	Fluidextract of ipecac	..	8.0	7.8	0.8	10.2	7.5	0.57	3.4	0.26
	Fluidextract of ipecac and steam	..	...	5.3	0.8	15.5	9.1	0.50	
	Fluidextract of ipecac, carbon dioxide and steam	..	8.2	6.0	0.9	14.5	14.3	0.86	1.13	0.07
R. B.	Fluidextract of ipecac	6	...	6.2	0.8	12.2			
	Fluidextract of ipecac and carbon dioxide	4	...	7.2	0.8	11.3			
	Fluidextract of ipecac	5	...	6.0	0.8	13.8			
	Fluidextract of ipecac, carbon dioxide and steam	2	...	7.0	0.8	12.2			
	Fluidextract of ipecac	6	...	6.0	0.9	14.1			

* Twelve examinations were made.

Inhalations of Oxygen (60 examinations).—Oxygen, administered either intranasally or by mask, regularly increased the viscosity of the sputum. The dried residue was increased during the administration of unhumidified oxygen and slightly decreased if the oxygen was first

TABLE 12.—*Influence on Sputum of Inhalations of Oxygen and of a Combination of an Expectorant Drug and Inhalations of Oxygen* *

Patient	Treatment	Viscosity, Seconds	p_H	Dried Residue, %	Ash		Total Nitrogen Content		Chloride Content	
					Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %
V. W.	None	42	...	8.2	0.9	10.6				
	Intranasally administered oxygen									
	2 hours	55	...	8.5	0.8	9.6				
	24 hours	70	...	7.4	0.9	12.2				
V. W.	Fluidextract of senega	14	...	6.8	0.8	11.0				
	Fluidextract of senega and oxygen (by mask)	92	...	9.3	0.9	10.0				
V. W.	Fluidextract of senega	24								
	Fluidextract of senega and oxygen (by mask)	75								
R. B.	None	3	...	5.8	0.8	13.3				
	Intranasally administered oxygen	4	...	4.9	0.6	13.0				
R. B.	None	3	...	6.8	0.8	11.5				
	Intranasally administered oxygen									
	24 hours	4	...	7.3	0.8	11.7				
	48 hours	6	...	8.1	0.8	9.5				
	None	2	...	6.8	0.8	10.6				
R. B.	None	2	...	6.0	0.9	14.3				
	Oxygen (by mask) 30 min.	3	...	6.4	0.7	11.7				
R. B.	None	2	...	7.1	0.8	11.1				
	Oxygen (by mask) 60 min.	3	...	7.1	0.7	10.5				
	Fluidextract of senega	2	...	7.2	0.8	10.7				
	Fluidextract of senega and intranasally administered oxygen	3	...	7.0	0.8	12.4				
R. B.	None	2								
	Oxygen (by mask) 60 min.	5								

* Sixty examinations were made.

passed through a water bottle. The amount of ash was either slightly lowered or unchanged. These results were not altered even if the patient was treated with an efficient expectorant drug at the same time (table 12).

Results of Bronchoscopic Examinations After Inhalations of Oxygen: In almost every case in which inhalations of oxygen were used the mucosa became pale and appeared dry. The amount of secretion, as estimated during the bronchoscopic examination, was slightly increased in comparison with that observed for the same patients without treatment. Secretions were more frothy and appeared to be more tenacious

TABLE 13.—*Influence of Inhalations of Oxygen on the Mucosa and Secretions of the Tracheobronchial Tree* *

Patient	Mucous Membrane	Sputum in Tracheobronchial Tree	
		Quantity	Quality
J. W.	.....	Small	Very thick; not foamy
	Normal	.....	Very thick; adherent
	Pale	Large	Frothy; viscous
E. M.	Red	Moderate	Unchanged
M. T.	Slightly red	Increased	Very thick
	Slightly red	Increased	Much more tenacious; adherent to walls
A. W.	Pale	Large	Usual
	Less red	Large	Thicker
E. L.	Normal	.....	Adherent to walls
	Pale	Large	High viscosity

* Ten examinations were made.

TABLE 14.—*Influence on Sputum of a Combination of Inhalations of Oxygen and Carbon Dioxide* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
V. W.	None.....	38	...	6.2	0.9	17.0			
	Steam, oxygen and carbon dioxide.....	14	...	5.1	0.9	17.2			
V. W.	None.....	24							
	Oxygen and 5% carbon dioxide	33							
R. B.	None.....	2							
	Oxygen and 5% carbon dioxide (60 minutes, by mask).....	3							

* Nineteen examinations were made.

than they did after administrations of carbon dioxide. This was the principal difference, and it was emphasized by the adherence of the secretions to the bronchial walls (table 13).

Inhalations of Oxygen with 5 per Cent Carbon Dioxide (19 examinations).—The addition of 5 per cent carbon dioxide to the oxygen did not inhibit the increase of viscosity produced by administration of

oxygen alone. The use of a combination of the two gases with inhalations of steam, however, lowered the viscosity and the dried residue of the sputum (table 14).

Results of Bronchoscopic Examinations After Inhalations of Oxygen and Carbon Dioxide: The action on the bronchial mucosa of carbon dioxide and oxygen in combination was irregular; in some cases there was reddening of the mucosa, while in others the mucous membranes

TABLE 15.—*Influence of Inhalation of 5 per cent Carbon Dioxide and 95 per cent Oxygen on Mucosa and Secretions of the Tracheobronchial Tree* *

Patient	Mucous Membrane	Sputum in Tracheobronchial Tree	
		Quantity	Quality
J. W.	Red	Increased	More liquid; adherent to walls
A. W.	Pale	Less copious	Slightly thicker but not tenacious
M. T.	Pale	Large quantity	Stringy and tenacious; frothy
M. T.	Redder, thicker	Increased	Tenacious but not adherent to walls

* Four examinations were made.

TABLE 16.—*Influence of Codeine Sulfate on Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Dried Residue, %	Ash		Total Nitrogen Content		Chloride Content	
					Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %
R. B.	None.....	3	...	5.8	0.8	13.3				
	Intranasally administered oxygen (24 hr.)	4	...	4.9	0.6	13.0				
	Codeine sulfate	5	...	6.7	0.8	12.5				
R. B.	None.....	5	...	6.0	0.8	12.4				
	Codeine sulfate									
	1st day.....	5	...	7.8	0.8	10.0				
	2d day.....	10	...	7.4	0.8	10.0				
	3d day.....	8	...	7.7	0.9	11.5				
R. B.	None.....	2	...	6.3	0.8	12.7				
	Fluidextract of senega.....	1	...	6.3	0.9	13.4				
	Fluidextract of senega and codeine sulfate									
	2d day.....	3	...	6.5	0.8	12.6				
	3d day.....	4	...	6.2	0.8	12.7				
	4th day.....	5	...	7.0	0.7	10.0				

* Twenty examinations were made.

appeared paler than normal. However, in every case the secretions became more copious, more liquid and definitely less gummy. The tendency for secretions to adhere to the bronchial walls noted previously with the use of oxygen alone was consistently absent when these gases were used in combination (table 15).

Codeine Sulfate (20 examinations).—The viscosity and the dried residue of the sputum became progressively increased from day to day.

This was also the case when codeine sulfate was used in combination with an efficient expectorant drug. There were no changes in the amount of ash (table 16).

Atropine Sulfate (10 examinations).—The effect of atropine sulfate was judged only by the results of bronchoscopic examinations, no special analyses of the sputum being made. The amount of sputum in the tracheobronchial tree in the patients examined was found to be uniformly less with administrations of atropine sulfate than without. Moreover, after aspiration of the superjacent mucopus the bronchi appeared to be uniformly clear. When the same patients were not treated with atropine, it was found uniformly that pus exuded continually from the smaller bronchial orifices during the bronchoscopic examination. In general,

TABLE 17.—*Influence of Atropine Sulfate on the Mucosa and Secretions of the Tracheobronchial Tree* *

Patient	Dose, Grains	Interval Between Administration of Drug and Bronchoscopic Examination	Appearance of Mucous Membrane	Secretions	
				Amount	Quality
A. W.	1/200	30 minutes	Slightly red	Usual	Less liquid, adherent
A. W.	1/150	60 minutes	Moist, red, very smooth	Usual	Less viscous
A. W.	1/150	60 minutes	Pale	Large	Very liquid †
M. T.	1/120	20 minutes	Red	No pus	Extremely thick
M. T.	1/120	40 minutes	Pale, moist	No secretion	
E. L.	1/150	15 minutes	Slightly red	Less	Copious †
G. W.	1/200	20 minutes	Slightly red	.....	Thick, adherent
T. T.	1/240	40 minutes	Pink, pale	Very little	Thick
A. K.	1/100	60 minutes	Very red	Decreased	Extremely thick
A. K.	1/150	30 minutes	Red	Decreased	Extremely thick

* Ten examinations were made.
† After aspiration of superjacent pus the bronchi appeared to be free of secretions.

the sputum was much more tenacious than it had been without treatment, and it even adhered to the mucosa. An associated observation was the decrease in the inflammatory character of the mucous membrane after the injection of atropine sulfate, the mucosa becoming paler. These effects were noticed as early as fifteen minutes after injection of the drug, but they reached their maximum later. The effect lasted at least one hour (table 17).

Influence of Medication and Inhalations on the First Portion of Sputum (18 examinations).—The dried residue content of the first portion was lower than that of the second portion from untreated patients and remained lower when fluidextract of senega and emetine hydrochloride were used. But after potassium iodine was administered the normal difference between the dried residue of the plug and that of the second portion of sputum disappeared. After treatment with

inhalations of steam and carbon dioxide, however, the dried residue of the plug was found to be much higher than that of the second portion.

TABLE 18.—*Influence of Medication and Inhalations on the First and Second Portions of Sputum**

Patient	Treatment	Viscosity, Seconds	p_H	Ash		Total Nitrogen Content		Chloride Content	
				Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %	Dried Residue, %	Total Sputum, %
N. C.	Potassium iodide								
	1st portion... ..		8.0	8.0	1.0	12.1	15.0	1.20	0.14	0.01
	2d portion.... ..		8.0	7.8	0.9	11.1	8.0	0.62	0.85	0.07
N. C.	Potassium iodide								
	1st portion... ..		7.8	7.2	1.0	13.1	12.5	0.90	12.02	0.92
	2d portion.... ..		7.8	7.2	0.8	11.4	7.6	0.60	7.0	0.57
N. C.	Fluidextract of senega								
	1st portion... ..		8.0	7.4	1.2	15.7	7.1	0.5		
	2d portion.... ..		8.0	7.6	1.0	12.7	10.7	0.8		
N. C.	Fluidextract of senega								
	1st portion... ..		8.0	8.0	1.0	12.2	11.0	0.9		
	2d portion.... ..		8.0	8.7	0.9	10.3	14.6	1.3		
N. C.	Fluidextract of senega								
	1st portion... ..		8.2	8.2	0.9	11.2	12.5	1.0		
	2d portion.... ..		8.2	8.2	0.9	10.5	9.7	0.8		
N. C.	Fluidextract of senega								
	1st portion... ..		7.8	7.5	1.0	13.7	9.7	0.7	1.37	0.10
	2d portion.... ..		7.8	7.7	0.9	11.5	7.2	0.6	0.57	0.04
N. C.	Fluidextract of senega								
	1st portion... ..		8.0	7.1	1.0	13.3	12.1	0.9		
	2d portion.... ..		8.0	7.9	0.9	11.5	9.3	0.7		
N. C.	Fluidextract of ipecac								
	1st portion... ..		...	9.5	0.9	9.0				
	2d portion.... ..		...	9.0	0.8	9.0				
N. C.	Fluidextract of ipecac								
	1st portion... ..		...	9.8	0.9	9.1				
	2d portion.... ..		...	8.7	0.9	10.3				
N. C.	Emetine hydrochloride								
	1st portion... ..		...	8.9	0.9	10.2				
	2d portion.... ..		...	9.0	0.9	9.9				
N. C.	Emetine hydrochloride								
	1st portion... ..		8.2	8.3	0.9	10.7				
	2d portion.... ..		8.2	9.4	0.8	8.6				
N. C.	Emetine hydrochloride								
	1st portion... ..		8.0	8.2	0.9	10.1				
	2d portion.... ..		8.2	8.7	0.9	10.0				
N. C.	Emetine hydrochloride								
	1st portion... ..		...	6.8	0.9	13.0	9.8	0.66		
	2d portion.... ..		...	7.6	0.9	12.3	9.4	0.71		
N. C.	Emetine hydrochloride								
	1st portion... ..		...	7.5	0.9	12.7				
	2d portion.... ..		...	8.0	0.9	11.2				
N. C.	Inhalations of steam								
	1st portion... ..		...	9.0	0.9	10.0				
	2d portion.... ..		...	7.1	0.9	12.3				
N. C.	Inhalations of steam								
	1st portion... ..		...	8.9	0.9	9.6				
	2d portion.... ..		...	7.4	0.9	12.1				
V. W.	Inhalations of carbon dioxide								
	1st portion... ..		...	9.1	0.9	10.4				
	2d portion.... ..		...	7.8	0.8	10.0				

* Seventeen examinations were made.

Since for untreated patients or for those treated with expectorants the reverse of these observations was noted, it appears that the plug was

not affected by the dilution which the steam or carbon dioxide caused in the second portion. Consequently, the plug remains essentially inert to treatment. The ash of the plug from untreated patients, which was lower than that of the second portion, was usually increased after the use of expectorants and remained the same after inhalations of steam or carbon dioxide. This indicates that the content of inorganic matter

TABLE 19.—*Influence of Medication and Inhalations on the Third Portion of Sputum* *

Patient	Treatment	Viscosity, Seconds	p_H	Ash: Dried Residue, %	Ash: Total Sputum, %	Total Nitrogen Content: Dried Residue, %	Total Nitrogen Content: Total Sputum, %	Chloride Content: Dried Residue, %	Chloride Content: Total Sputum, %
V. W.	Potassium iodide								
	Cough †	27	...	6.0	...	....	13.1	0.78	
	Bron.†	..	...	9.5	...	....	14.4	1.32	
N. C.	Fluidextract of senega								
	Cough	..	...	8.5	0.9	11.2			
	Bron	..	...	8.0	0.9	11.3			
N. C.	Ipecac								
	Cough	..	...	8.5	0.9	11.2			
	Bron	..	...	8.0	0.9	11.3			
N. C.	Emetine hydrochloride								
	Cough	..	...	8.0	0.8	9.9	13.1	1.05	
	Bron	..	..	6.9	0.9	13.0	17.8	1.22	
N. C.	Emetine hydrochloride								
	Cough	..	8.0	8.0	0.9	11.2	6.5	0.52	
	Bron	..	8.0	7.2	0.9	13.0	12.7	0.92	
V. W.	Emetine hydrochloride								
	Cough	..	8.0	8.7	0.8	9.1	10.5	0.91	
	Bron	..	8.0	9.5	0.9	9.2	10.0	0.96	
V. W.	Emetine hydrochloride								
	Cough	..	8.0	7.8	0.7	9.1	11.3	0.88	
	Bron	..	8.0	10.0	0.9	9.0	10.0	1.00	
V. W.	Inhalations of carbon dioxide								
	Cough	20	...	8.4	0.8	10.0	16.5	1.39	
	Bron	..	...	10.8	0.9	8.2	16.3	1.76	
V. W.	Inhalations of steam and emetine hydrochloride								
	Cough	..	...	9.3	0.7	16.2	9.6	0.20	
	Bron	..	...	7.6	0.9	11.3	8.7	0.66	
V. W.	Inhalations of carbon dioxide and steam								
	Cough	4	...	9.4	0.7	19.6	8.9	0.39	
	Bron	..	...	10.0	0.9	9.2	20.7	2.07	

* Nine examinations were performed.
† "Cough" means that the specimen was coughed up and "Bron." that it was obtained with a bronchoscope.

of the plug is not influenced by inhalations of steam and carbon dioxide but is influenced by the use of expectorants and gases. The effect on viscosity was not determined, because the amount of sputum obtained was always too small (table 18).

Influence of Medication and Inhalations on the Third Portion of Sputum (9 examinations).—The dried residue of the third portion is higher than that of the second portion for untreated patients. Since

after the use of drugs the dried residue of the second portion increases, the fact that the dried residue of the third portion is then lower indicates that the third portion is not actually influenced by expectorant drugs.

Furthermore, by use of inhalations of steam and carbon dioxide the dried residue and the amount of ash of the second portion are markedly reduced, while the ash and dried residue of the third portion are not changed. Therefore, the third portion again does not participate in the changes which are effected in the second portion by inhalations of carbon dioxide and steam (table 19).

Effect of Inhalations of Carbon Dioxide on the Hydrogen Ion Concentration of the Blood (2 examinations).—The result of the first examination was as follows: At 10:40 a. m. the p_H of the blood was 7.42. Inhalations of carbon dioxide were given at the rate of 3.5 liters per minute, and at 11:00 a. m. the p_H of the blood was 7.48. The results of the second examination were as follows: At 10:40 a. m. the p_H of the blood was 7.51. Inhalations of carbon dioxide at the rate of 3.5 to 4 liters per minute were given, and at 11:10 a. m. the p_H of the blood was 7.30, and at 11:15 a. m. it was 7.55.

The determinations of the p_H of the blood were made before and immediately after the inhalations of carbon dioxide. They showed that the effect on the hydrogen ion concentration disappears shortly after the inhalations are discontinued.

COMMENT

It was demonstrated in part 1 of this study that under "natural," or physiologic, conditions changes in the sputum which can be observed clinically may be measured or evaluated by the changes in its physical and chemical properties. One is justified, therefore, in interpreting the changes in the physical and chemical properties of sputum as a measure of the efficiency of an expectorant. The methods herein employed give evidence about the changes in the expectorated sputum, about the changes in that portion of the bronchial secretion which lies in the deeper parts of the tracheobronchial tree long before expectoration and about the condition of the bronchial mucosa. No results have been obtained relative to the influence of expectorants on the bronchial muscles. Again the amount of expectorated sputum is not to be considered as a measure of the effect of treatment—not only because of the inaccuracies involved in measuring or weighing sputum but, what is more important, because of the resorption of sputum under the influence of expectorants. Such resorption has been previously described,[4] and that it occurs has also been confirmed by us.

Expectorants are supposed to have specific actions on different types of pathologic secretion. According to our observations, however, it is

not possible to note any specific differences in their influence on the studied characteristics of sputum; that is, all of the drugs studied apparently influenced the various physical and chemical properties we examined in about the same manner and to about the same degree. Therefore, they may be discussed in one group.

The most constant and impressive influence noted was the lowering of the viscosity of the sputum. This was regularly observed after administration of the drugs in spite of the inconstant results with regard to the chemical qualities of the sputum. This is the most important clinical aspect of the use of expectorants.

A surprising observation is the irregularity of the effects on the chemical qualities of sputum in spite of a constant physical change (dilution) with the use of expectorants. Previous work has demonstrated that the changes (liquefaction) of sputum by natural processes, such as those which occur in the tracheobronchial tree of untreated patients, do not show a parallel between viscosity and the content of solid substances of the sputum. Moreover, certain parts of the expectorant drug are secreted into the sputum through the tracheobronchial mucosa and further irregularly influence the chemical properties of the sputum. The p_H is lowered in some instances (after administration of ammonium chloride or potassium iodide), is not influenced in some instances (with the use of ipecac or saponins) and is even increased after the subcutaneous injection of emetine hydrochloride. The dried residue is increased only after the administration of ammonium chloride and saponins and is not regularly influenced by the use of potassium iodide, ipecac or emetine hydrochloride in all patients. Again, these results are similar to those obtained in cases in which no drug therapy was used, in that the sputum may become liquefied without consistent changes in the amount of solid substances taking place. The amount of ash was influenced only insignificantly by the use of expectorant drugs. The content of total nitrogen of the sputum was regularly and markedly higher after the administration of ammonium chloride, was increased to a lesser degree after the administration of the saponins, was only occasionally higher after the use of ipecac and was fairly regularly increased after the use of emetine hydrochloride. Potassium iodide produced no consistent change in this respect.

Definite proof of the influence of steam on the character of the bronchial mucosa and on the qualities of the sputum in the bronchi has, in the past, been lacking. The influence of other gases on these properties has likewise been little studied. Our observations show that inhalations of gas (steam or carbon dioxide) act as a real expectorant by diluting the sputum, that is, by lowering its viscosity and reducing all of the examined solid contents. In comparing the physical and

chemical properties after the use of such inhalations with the same properties after the administration of drugs one at once realizes the greater liquefaction of the sputum produced by use of the gases. Since in this treatment there is no interference with the chemical properties of the sputum through secretion of the administered drugs into it, the dried residue, the amount of ash and the total nitrogen content are regularly markedly lowered. Combined inhalations of steam and carbon dioxide proved to be still more effective in liquefying secretions than the use of either gas alone, and the best results were obtained by using expectorant drugs with this combination of steam and carbon dioxide. As far as the chemical qualities of the sputum are concerned, the addition of drugs to the combination increases the dried residue and the total nitrogen content because of the actual secretion of the drugs into the sputum (table 20).

The effect of carbon dioxide on the chemical and physical qualities of sputum itself is essentially the same as that of inhalations of steam.

TABLE 20.—*Comparison of Effects of Different Kinds of Treatment on Sputum*

Treatment	p_H	Viscosity	Dried Residue	Ash	Total Nitrogen Content
Steam	Irregular	−−	−−	−	−−
Carbon dioxide	..	−−	−−	−	−
Drugs and steam	..	−−−	±	0	±
Carbon dioxide and steam	+	−−−−	−−−	−−	−−−
Carbon dioxide, steam and drugs	+	−−−−−	Irregular	0	

However, bronchoscopic examination of patients who had been treated by inhalations of carbon dioxide showed that this gas had a specific influence on the mucous membranes of the tracheobronchial tree. Definite hyperemia was observed. This reaction was, as a rule, limited to the portion of the tracheobronchial tree which was most involved by the pathologic process. Only small amounts of liquefied sputum were obtained from the tracheobronchial tree after administration of this gas in spite of the fact that the patients had not coughed up an appreciable amount of sputum during the inhalations. The patients had been subjected to repeated bronchoscopic examinations without the inhalations of carbon dioxide prior to the examination after the inhalations, and consequently we feel justified in comparing the amounts of sputum observed in the tracheobronchial tree in these experiments, particularly since the range of quantities was extreme rather than small.

This reduction in the amount of sputum in the tracheobronchial tree is explained by an increase in resorption. This increase is caused by hyperemia and a rise in the respiratory rate, as was mentioned previously.

Thus, carbon dioxide must be considered as an expectorant because it liquefies the sputum, stimulates the cough reflex and causes an increase in the resorption of the sputum within the tracheobronchial tree. The mechanism of the pharmacologic action of carbon dioxide may be summarized as follows: (1) increase in the respiratory rate, (2) liquefaction (dilution) of the sputum, (3) irritation of the mucous membrane (only of the part involved by the pathologic process), (4) increase of resorption of sputum and (5) stimulation of the cough reflex. These actions take place without any lasting changes in the p_H of the blood being effected. A sufficient number of clinical observations has demonstrated that the use of this gas, either alone or in combination with steam and drugs, is an efficient agent for clearing the tracheobronchial tree.

Oxygen has been used therapeutically for many well known purposes. Its influence on the physical and chemical properties of sputum, however, has not been studied. Clinical observations have led us to avoid its use in cases of acute obstructive laryngotracheobronchitis because of the resultant apparent desiccation of secretions.

Our experimental investigation showed that oxygen acts in a manner opposite to that of expectorants (especially carbon dioxide) in that it increases the viscosity of the sputum and its dried residue. It is only when oxygen which has been passed through a water bottle is used that the dried residue of the sputum becomes slightly lowered, and the viscosity is increased to the same extent as when the oxygen is administered without being humidified. The results of bronchoscopic examinations further confirmed the clinical impression and the observations on the sputum. Consistent pallor of the mucosa was associated with an apparent drying of the secretions, which then became adherent to the walls of the bronchi. This adherence of the mucus to the bronchial walls was not noticed consistently with any other treatment or when the patient was not treated. The influence of oxygen is extremely strong, and it is not neutralized by the addition of 5 per cent of carbon dioxide or the use of an efficient expectorant. However, the addition of inhalations of steam and carbon dioxide to the administration of oxygen neutralized this drying effect.

In view of these results we are justified in considering inhalations of oxygen as an antiexpectorant.

Codeine is used in a large number of expectorant mixtures (cough medicines). For this reason, studies regarding its influence on the physical and chemical properties of sputum were indicated. It was found that the use of codeine sulfate increased the viscosity and the dried residue of sputum. This influence was progressively greater the longer the drug was used. Even when an efficient expectorant was used in addition the influence of the codeine was predominant. Therefore,

codeine sulfate not only suppresses the cough reflex, which is sometimes desirable or an aim of treatment, but acts as an antiexpectorant with respect to the qualities of the sputum, which is not a desirable aim of treatment.

The thickening of secretions in the tracheobronchial tree caused by the use of atropine sulfate is an established experimental and clinical fact. It was confirmed by bronchoscopic examinations, which showed that the secretions were uniformly thickened. Associated with this, and possibly responsible for it, was pallor of the mucosa. The apparent cessation of production of mucus was surprisingly apparent. Aspiration of the loose mucopus in the trachea and larger bronchi of patients who previously had had large quantities of secretion in the tracheobronchial tree left the bronchi clear, and relatively little additional secretion appeared in the main bronchi from the smaller divisions.

In the first part of this study we described the presence of a mucus plug on top of the secretions of the tracheobronchial tree in some patients with bronchiectasis. The examinations of the influence of expectorants on this plug showed that the usual expectorants, carbon dioxide, steam and potassium iodide, do not influence its content of organic and inorganic material. However, these expectorants definitely do influence the main portion of the secretions, previously designated as the second portion. Only fluidextract of senega and emetine hydrochloride seem to have some influence on the plug; apparently they affect it in the same manner in which they influence the second portion.

The third type of sputum, which is found in the most dependent portion of the tracheobronchial tree and is obtained only by bronchoscopic suction after the superjacent pus is aspirated, has been described previously. This extremely thick, viscid secretion, lying deep in the bronchi, is never coughed up. Its physical and chemical qualities cannot be influenced by expectorants or inhalations, even though the superjacent, or second, portion is influenced by such agents.

SUMMARY

The influence of various drugs and gases on the sputum and certain properties of the tracheobronchial tree were studied by determination of the physical and chemical properties of the sputum and bronchoscopic observation of the intrabronchial changes which followed therapy.

The expectorant drugs ammonium chloride, potassium iodide, fluidextract of senega, fluidextract of ipecac and emetine hydrochloride liquefied the sputum consistently, as was evidenced by a decrease in the measured viscosity. According to our determinations, there was no difference in the efficacy of these drugs with regard to liquefaction.

Inhalation of steam liquefies the sputum more efficiently than do the expectorant drugs; this liquefaction is effected by a great reduction in its viscosity. The content of organic and inorganic substances is also reduced. Thus the action is one of simple dilution.

Inhalations of carbon dioxide serve as a most efficient expectorant. Such inhalations reduce the amount of sputum within the bronchial tree by stimulating resorption and render the remainder more liquid, so that it is coughed up more easily. Therefore, one is entitled to regard inhalations of carbon dioxide as a "new" expectorant.

The most efficient therapeutic regimen which may be initiated to clear the bronchial tree of its pathologic secretions was found to be a combination of inhalation of carbon dioxide and steam and administration of expectorant drugs.

The influence of inhalations of oxygen on the sputum itself has been found to be opposite to that of an expectorant, and consequently oxygen may be regarded as an antiexpectorant. It increases the viscosity of the sputum most markedly and likewise increases its content of solid substances. The sputum becomes not only thicker but adherent to the mucous membrane. This undesirable influence of the otherwise useful inhalations of oxygen cannot be compensated for by giving oxygen in combination with the usual 5 per cent admixture of carbon dioxide. Only the addition of sufficient moisture to a mixture of these two gases will equalize the discovered disadvantage of the inhalations of oxygen. Whether the addition of 10 per cent of carbon dioxide will serve this purpose has not been studied. These results must be carefully considered when oxygen is to be employed therapeutically, for instance, when it is to be administered in cases of acute laryngotracheobronchitis or bronchial asthma.

Codeine sulfate may also be considered as an antiexpectorant, because it increases the viscosity of the sputum. Its use in combination with an expectorant drug does not impair the efficiency of the expectorant for the first twenty-four hours. After this, the viscosity of the sputum and its content of solid substances are gradually but definitely increased. Therefore, codeine sulfate must not be used with an expectorant if dilution of the sputum is the therapeutic objective.

Atropine sulfate has been found to act as an antiexpectorant, by decreasing the production of sputum and markedly increasing the viscosity of the unexpectorated material.

The secretion in the most dependent portion of the tracheobronchial tree and the plug noted on the top of the column of secretion are not affected by expectorants.

The results of using inhalations of carbon dioxide in cases of pertussis, in which a most tenacious type of sputum is produced, remain to be studied. Likewise, the efficacy of carbon dioxide as a liquefying agent in cases of purulent sinusitis must be considered.

FACTORS INFLUENCING RETENTION OF NITROGEN AND CALCIUM IN PERIOD OF GROWTH

V. FURTHER EVIDENCE OF THE ANABOLIC EFFECT OF THYROID ON CALCIUM METABOLISM

JOSEPH A. JOHNSTON, M.D.
DETROIT

The role of the thyroid gland in the period of growth is anabolic. The retention of calcium and nitrogen being used as a measure of the effect of thyroid, it was previously shown[1] that maximal positive balances were obtained with a normal metabolic rate and that when the rate was depressed below or elevated above the normal there were accompanying diminutions in the retention of these two substances. In the case of nitrogen, it is doubtful that this effect is either large or specific. An increase in the absorption and oxidation of carbohydrate may be the primary result and a slight sparing of protein the secondary. There is, however, the added effect of increased appetite and intake of food, which results in a higher retention of nitrogen. In a long observation on cretins the negative balances observed when the metabolic rate was at its lowest were in part referable to refusal of food and the positive balances when thyroid had exerted its peak effect to a higher intake of nitrogen. In the case of calcium, there is an actual increase in the percentage utilization of a given intake, referable largely to diminished fecal excretion, when thyroid is given to a growing child whose metabolic rate is below normal in amounts sufficient to bring it up to normal; larger amounts will reverse this situation and diminish the retention.

Depressions of the basal metabolic rate caused by factors other than primary involvement of the thyroid gland are well recognized. The results of a study of the lowered metabolism of subjects on submaintenance diets were reported previously.[2] The fall in rate which occurs with inactivity is likewise well recognized. With the latter condition a

From the Henry Ford Hospital.

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2. Johnston, J. A., and Maroney, J. W.: Relationship of Basal Metabolism to Dietary Intake, Am. J. Dis. Child. **51**:1039 (May) 1936.

loss of sulfur, nitrogen, phosphorus and calcium has been reported by Cuthbertson [3] for 8 subjects with noninfectious orthopedic conditions during periods of rest in bed ranging from eleven to forty-eight days. The sulfur nitrogen ratio suggested a sulfur-rich source of the excreted material, presumably for the most part muscle. Oxygen consumption fell slightly. On the other hand, muscle work has been shown by Cathcart and Burnett [4] to produce a rise in the nitrogen output of a subject whose basal metabolic rate was apparently normal at the beginning of the observation. The loss of nitrogen was least when the diet was high in protein. The results of both of these studies are comparable to those of the studies on thyroid, which showed that losses occurred when the basal metabolic rate was either elevated above or depressed below the normal.

The atrophy of bone resulting from disuse is a well recognized phenomenon. Allison and Brooks,[5] in their animal work, showed a frank diminution in the amount of mineral, but the percentage per unit of bone was unchanged.

The improvement in the carbohydrate metabolism of the diabetic subject [6] with exercise is pertinent, since carbohydrate metabolism is inseparable from nitrogen metabolism.

Whether or not with rest in bed and a fall in metabolic rate there actually occurs an atrophic change in the glands governing metabolism is not clear, though Plummer expressed the belief that with the fall incident to an inadequate intake of food such a change did occur in the thyroid. In the hibernating animal actual cytologic change, which is capable of reversal with activity, apparently can be demonstrated in the pituitary.

The use of prolonged rest in bed in the management of a number of conditions with which exercise has seemed undesirable or impossible made it seem worth while to study the effect of elevating the metabolic rate, by the administration of thyroid, in 2 patients whose hospitalization extended over long periods, of nineteen months and thirty-one months respectively. In the first case (paralysis following poliomyelitis) the element of infection was absent as a variable; in the second case, tuberculosis complicated the effects of the element of rest.

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3. Cuthbertson, D. P.: The Influence of Prolonged Muscular Rest on Metabolism, Biochem. J. **23**:1329, 1929.

4. Cathcart, E. P., and Burnett, W. A.: The Influence of Muscle Work on Metabolism in Varying Conditions of Diet, Proc. Roy. Soc., London, s.B **99**:405, 1925-1926.

5. Allison, N., and Brooks, B.: Bone Atrophy, Surg., Gynec. & Obst. **33**:250 (Sept.) 1921.

6. Hetzel, K. S., and Long, C. N. H.: The Metabolism of the Diabetic Individual During and After Muscular Exercise, Proc. Roy. Soc., London, s.B **99**:279, 1925-1926.

EXPERIMENTAL OBSERVATIONS

The metabolism studies consisted of continuous determinations of the calcium and nitrogen balances with concurrent determinations of the basal metabolic rate for the entire time. The six rotating diets which were employed were analyzed weekly for their content of calcium and nitrogen. Details of the technic employed were given in the first two papers of this series. The results are given in the charts as curves smoothed by the method of three's, using twelve day averages. In the tables the data are recorded as six day averages for P. R. but as eighteen day averages for R. C., who was under observation for more than a year.

Two preparations of thyroid were used, those of Burroughs, Wellcome and Company and Parke, Davis and Company. It has been considered that 1 grain (0.06 Gm.) of the Burroughs, Wellcome preparation is equivalent in strength to ⅙ grain (0.012) of the Parke, Davis thyroid.

OBSERVATION.—P. R., an 11 year old girl, was first seen in the acute stage of poliomyelitis with involvement of both legs, in December 1937. During the following sixteen months she was confined to bed. Whirlpool baths were started in April 1938 and passive massage in May. She was transported to the school on the hospital grounds on a stretcher. In April 1939 she walked a short part of each day on crutches.

The metabolism study extended from Jan. 21 to June 30, 1939, a total of one hundred and sixty-one days. It was our plan in all of this work to ascertain before starting the balances the amount of food which could be taken with appetite. P. R.'s appetite was extremely capricious, and she refused an intake of more than 1,500 calories per day. Her basal calories in the control period of twenty-nine days averaged 1,173, but in the presence of paralysis of both lower extremities determining the amount of active protoplasmic tissue is impossible and accordingly the metabolic rate could only be conjectured. For a normal child of this height and weight the average of the first four determinations of basal metabolic rate would be interpreted as —19 per cent by the Boothby surface area standard and —5 per cent by the Talbot height standard.

She was very pale and apathetic. The hemoglobin content was 11.8 Gm. per hundred cubic centimeters, and the red blood cells numbered 4,280,000 per cubic millimeter. The cholesterol content of the blood was 160 mg. per hundred cubic centimeters. The bone age was approximately normal by Todd's standards. The femurs showed definite osteoporosis.

Thyroid was given daily in the following amounts: period 2, 1 grain (0.06 Gm.) of the Burroughs, Wellcome preparation (equivalent to ⅙ grain [0.012 Gm.] of the Parke, Davis product); period 3 sixty days, 2 grains (0.12 Gm.) of the Burroughs, Wellcome preparation, and periods 4 and 5, 1 grain of Parke, Davis thyroid.

Analysis of the diet gave practically constant results except for the usual slight seasonal variations until period 5, when it was possible because of definitely increased appetite to increase the intake to 1,900 calories daily, with proportionate increases in nitrogen and calcium. In the final six day period she took 2,200 calories daily.

When administration of thyroid was started there was a slight fall in total basal calories, a phenomenon which my associates and I have noted previously in studies on cretins and which has been observed in the case of patients with myxedema.

TABLE 1.—*Effect of Thyroid on Nitrogen and Calcium Balances of P. R.*

Medication	Period	Date	Nitrogen, Gm.				Calcium, Gm.				Total Calories	Respiratory Quotient	Weight, Pounds	Height, Inches	Percentage Retention		Dietary Calories
			Urine	Stool	Intake	Balance	Urine	Stool	Intake	Balance					Nitrogen	Calcium	
None.....	1	1/21-25	6.78	1.33	9.00	+0.89	0.028	0.500	0.840	+0.222	1,255	0.77	105	59			
		1/26-31	7.20	0.92	9.45	+1.33	0.046	0.580	0.870	+0.244	.....	....	...	..	..	..	1,500
		2/1-6	7.36	1.01	9.90	+1.53	0.050	0.622	0.900	+0.228	1,144	0.81	97				
		2/7-12	7.00	1.15	9.90	+1.75	0.025	0.597	0.900	+0.278	1,177	0.80					
		2/13-18	6.70	0.90	9.90	+2.30	0.020	0.629	0.900	+0.251	1,114	0.81	96¼				
	Average.....		7.01	1.05	9.65	+1.58	0.034	0.604	0.883	+0.245	1,173	0.80	..	..	16	27	
Thyroid (B. W.) 1 grain daily	2	2/19-24	7.93	0.99	8.94	+0.02	0.025	0.677	0.861	+0.169	1,140	0.81	96½				
		2/25-3/2	7.10	1.35	9.60	+1.15	0.026	0.628	0.885	+0.231	1,076	0.77	95				
		3/3-8	7.39	0.97	9.60	+1.24	0.031	0.645	0.920	+0.244	1,078	0.84	95½				
	Average.....		7.47	1.10	9.38	+0.80	0.027	0.647	0.889	+0.215	1,098	0.81	..	..	8	25	
Thyroid (B. W.) 2 grains daily	3	3/9-14	7.38	0.72	9.82	+1.72	0.031	0.467	0.930	+0.432	1,128	0.83	95				
		3/15-20	7.64	1.17	9.97	+1.16	0.037	0.642	0.893	+0.214							
		3/21-26	7.51	1.06	9.90	+1.33	0.045	0.620	0.885	+0.220	1,214	0.89					
		3/27-4/1	6.89	0.90	9.93	+1.96	0.040	0.575	0.900	+0.285	1,203	0.83	96				
		4/2-7	8.22	1.22	9.82	+0.38	0.039	0.623	0.900	+0.238	1,161	0.88	94½				
		4/8-13	7.26	0.56	9.98	+2.16	0.034	0.385	0.915	+0.496	1,212	0.93					
		4/14-19	7.34	0.74	10.05	+1.97	0.033	0.505	0.938	+0.399	1,101	0.79	95				
		4/20-25	6.49	0.54	10.05	+3.02	0.033	0.394	0.945	+0.518	1,148	0.91	94½				
		4/26-5/1	7.60	0.76	9.98	+1.62	0.043	0.631	0.885	+0.211							
		5/2-7	7.25	0.57	9.90	+2.08	0.035	0.447	0.885	+0.403	1,079	0.82	95	60			
	Average.....		7.36	0.82	9.92	+1.74	0.037	0.529	0.908	+0.342	1,156	0.86	..	..	17	37	
Thyroid (P. D.) 1 grain daily	4	5/8-13	7.77	0.88	9.90	+1.25	0.031	0.679	0.885	+0.175	1,162	0.87	94½	60½			
		5/14-19	8.90	0.95	9.75	−0.10	0.048	0.663	0.900	+0.189	1,260	0.78	92¾				
		5/20-25	9.30	0.88	9.90	−0.28	0.043	0.569	0.915	+0.303	1,073	0.81	93¼				
		5/26-28	8.11	0.88	10.05	+1.06	0.043	0.563	0.930	+0.324							
	Average.....		8.58	0.90	9.88	+0.40	0.041	0.626	0.904	+0.237	1,165	0.82	..	..	4	26	
	5	5/29-6/3	10.08	1.03	12.92	+1.81	0.048	0.913	1,273	+0.312	1,187	0.78	93	60½			1,900
		6/4-9	10.28	0.80	13.20	+2.12	0.064	0.674	1.273	+0.535	1,234	0.75					
		6/10-15	10.55	1.14	12.83	+1.64	0.062	1.019	1.273	+0.192	1,160	0.77					
		6/16-21	9.66	0.96	12.59	+1.97	0.060	0.808	1.178	+0.310	1,234	0.81					
		6/22-24	10.02	0.94	12.54	+1.58	0.060	0.780	1.254	+0.414	.....	....					
	Average.....		10.01	0.98	12.84	+1.85	0.058	0.845	1.249	+0.346	1,204	0.78					
	6	6/25-30	10.64	1.06	14.52	+2.82	0.062	0.721	1.453	+0.669	1,304	0.89	95	61½	19	46	2,200

During the third period of sixty days, the total basal calories showed little consistent change, though one observation showed a rise to 1,260 calories. There was, however, a definite increase in the retention of calcium, referable largely to a diminished fecal loss. The slight increase in nitrogen is possibly not significant, though, with a rise in the respiratory quotient from an average of 0.81 to 0.86, it might be argued that a slight increase in carbohydrate oxidation had exerted its sparing effect on nitrogen.

In the fourth period an increase in the dose of thyroid to 1 grain of the Parke, Davis preparation was followed by a fall in the retention of both nitrogen and calcium.

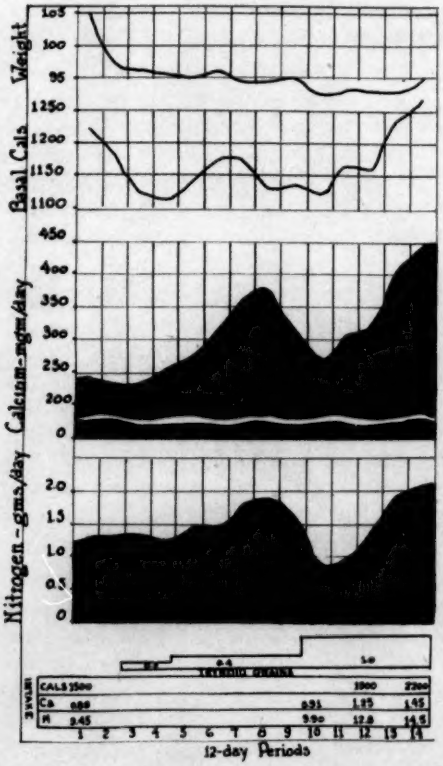

Chart 1.—Data for P. R., who was at rest in bed for nineteen months after an attack of poliomyelitis. The data have been averaged for twelve day periods, and these averages have been smoothed by the method of threes. With a fixed intake of food optimal retention occurred when 0.2 grains of thyroid was administered daily. With a daily dose of 1 grain the retentions diminshed, but they again increased with a higher intake of food, which had been refused at the beginning of the observation. The retentions in the control period are about half those previously noted for girls of this age.

In the fifth period the thyroid dosage remained the same but the intake of food was increased, and the highest balances of the study were attained save for those in the final, too short to be significant, period, when further increases in intake were impossible until after thyroid had been given.

I am at a loss to account for the very wide scatter in the values for basal metabolic rate obtained for a subject who was perfectly cooperative, and I wonder whether anything inherent in the process of muscle recovery may have influenced this variation. It is clear from the observations in the other studies in this series that a good deal of fluctuation can be expected in the premenarcheal years, and this child menstruated for the first time about eight months after the conclusion of this study.

It is concluded from this experiment that thyroid administered in small doses to a growing patient whose metabolism had presumably fallen with prolonged rest in bed resulted in an improved retention of calcium with but little effect on the retention of nitrogen so long as intake was constant, that larger doses definitely lowered nitrogen retention, though the calcium balances were about those of the control period, but that after improvement in appetite, which resulted in a larger intake, actual retentions of both substances were increased. With intake constant the percentage utilization of calcium was 27 in the control period, 25 with the administration of 1 grain of Burroughs, Wellcome thyroid, 37 with the administration of 2 grains of Burroughs, Wellcome thyroid and 26 with the administration of 1 grain of Parke, Davis thyroid.

By way of comparison, the retentions of 3 normal girls at just this age level (the year preceding the menarche, which in the case of P. R. occurred six months after these observations) were determined. The daily intake of nitrogen ranged between 12 and 14 Gm., with retentions between 2.02 and 4.07 Gm.; the daily intake of calcium ranged between 1.240 and 1.400 Gm., with retentions between 0.340 and 0.649 Gm.

Observation 2.—R. C., a girl born May 11, 1926, was found to have a positive reaction to tuberculin at the age of 5 years, and during the follow-up examination, at 10 years of age, she was found to have a minimal reinfection type of tuberculosis involving the upper lobe of the left lung. In May 1937 the menarche occurred. She returned to the hospital in 1938, at the age of 12 years, because of an exacerbation of the pulmonary lesion, and pneumothorax was instituted. A metabolism study was carried out over the period from September 1938 through August 1939.

During the first two hundred days of the observation the basal metabolic rate fell, the lowest value being —29 per cent by the surface area standard of Boothby or —24 per cent by the Talbot height standard. Nitrogen retention declined from a high of 2 Gm. per day to 0.5 Gm. per day. Calcium retention ranged between 0.066 and 0.426 Gm. per day, with an average of 0.247 Gm.; the retentions when plotted in eighteen day periods showed a cyclic tendency.

Thyroid was administered at three levels of dosage: (1) 1 grain of the Burroughs, Wellcome preparation (equivalent to ⅓ grain of Parke, Davis thyroid) through periods 13, 14 and 15; (2) 1 grain of the Parke, Davis preparation through periods 16, 17 and 18, and 2 grains of the Parke, Davis preparation in periods 19 and 20.

While the interpretation of the pulmonary changes that occurred during this time is difficult because of the pneumothorax, the collapse of the lung was not

complete enough to interfere greatly, and three independent readings of the roentgenograms for evidence of the disease were in agreement. The interpretations of Dr. Bruce Douglas are as follows:

"Aug. 30, 1938: There is a mixed type of infection in the upper third of the left lung. There is no definite evidence of a cavity, but the appearance of the lesion beneath the clavicle suggests that it is beginning to break down. Just beneath the clavicle are irregular calcifications suggesting an old primary focus lying in the midst of the new reinfection lesion.

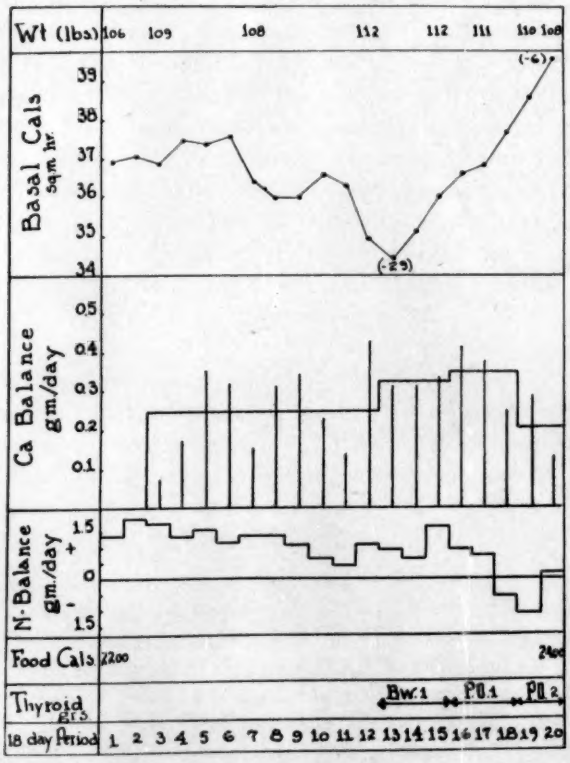

Chart 2.—Data for R. C. Each bar in the calcuim balance represents data for an eighteen day period. These are averaged and grouped under separate blocks for the control period and for the three periods during which three amounts of thyroid were used. The percentage utilization of calcium increased from 18.6 to 26.9 with the optimal dosage of 1 grain of the Parke, Davis preparation daily and diminshed with the use of 2 grains. There was a slight improvement in nitrogen retention with administration of the smallest dose of thyroid and a decrease when a larger amount was used.

"Sept. 15, 1938 (period 1): There is a small amount of air over the apical area, extending to the level of the fourth rib in the mammary line. The calcifications previously noted are of the same extent and appearance.

TABLE 2.—*Effect of Thyroid on Nitrogen and Calcium Balances of R. C.*

Medication	Period	Date	Nitrogen, Gm.				Calcium, Gm.				Basal Metabolic Rate,* per Cent		Respiratory Quotient	Calories per Sq. M. per Hour	Total Calories	Weight, Pounds	Height, Inches	Percentage Retention		Dietary Calories
			Urine	Stool	Intake	Balance	Urine	Stool	Intake	Balance	B	T						Calcium	Nitrogen	
None	1	9/10-27	11.35	1.29	13.99	+1.35	.....	.....	.....	.....	—16	—11	0.77	36.9	1,345	106	65	....	...	2,200
		9/28-10/15	11.50	1.10	14.52	+1.92	.....	.....	.....	.....	—16	—11	0.74	36.9	1,348	109				
		10/16-11/2	11.63	1.28	14.67	+1.76	0.133	1.132	1.331	0.066	—15	— 9	0.75	37.4	1,372	109				
		11/3-20	12.14	1.30	14.75	+1.31	0.088	1.048	1.331	0.175	—11	—11	0.75	36.4	1,345	109				
		11/21-12/8	11.71	1.34	14.61	+1.56	0.071	0.974	1.386	0.341	—12	— 5	0.79	38.8	1,428	110				
		12/9-26	11.91	1.21	14.29	+1.17	0.077	0.977	1.351	0.297	—16	—11	0.78	36.9	1,347	108½				
		12/27-1/13	11.24	1.19	13.73	+1.30	0.072	1.015	1.239	0.151	—15	— 9	0.79	37.0	1,361	109				
		1/14-31	11.46	1.10	13.94	+1.38	0.075	0.957	1.351	0.318	—20	—14	0.77	35.3	1,294	107				
		2/1-18	12.10	1.14	14.32	+1.08	0.054	0.921	1.315	0.340	—19	—13	0.75	35.7	1,304	109				
		2/19-3/12	12.23	1.23	14.15	+0.69	0.060	0.995	1.279	0.224	—16	—10	0.79	37.1	1,358	110				
		3/13-30	12.48	1.23	14.19	+0.48	0.037	1.147	1.320	0.136	—16	— 9	0.79	36.9	1,370	110¾				
		3/31-4/17	12.31	1.00	14.39	+1.08	0.058	0.862	1.346	0.426	—20	—15	0.80	34.8	1,288	112				
		Average....	11.84	1.20	14.29	+1.26	0.072	1.000	1.325	0.247	—16	—10	0.77	36.8	1,346	...	..	18.6	8.8	
Thyroid (B. W.), 1 grain daily	2	4/18-5/5	12.26	1.14	14.30	+0.90	0.049	0.986	1.325	0.290	—23	—18	0.80	33.0	1,236	112½	65¼			
		5/6-5/23	12.66	1.14	14.44	+0.64	0.063	0.944	1.320	0.313	—17	—12	0.83	35.4	1,327					
		5/24-6/4	11.52	1.27	14.47	+1.68	0.086	1.000	1.418	0.332	—16	—10	0.78	37.0	1,383	112½	66			
		Average....	12.22	1.17	14.39	+1.00	0.063	0.973	1.346	0.310	—19	—13	0.80	35.0	1,315	...	..	24.0	7.8	
Thyroid (P. D.), 1 grain daily	3	6/5-22	12.76	1.01	14.74	+0.97	0.088	0.894	1.401	0.419	—19	—12	0.75	35.5	1,340	111¼	66			
		6/23-7/10	12.04	1.04	13.83	+0.75	0.075	0.871	1.320	0.374	—15	— 9	0.79	37.4	1,397					
		7/11-22	12.93	1.26	13.64	—0.55	0.066	0.938	1.248	0.244	—15	— 9	0.76	37.5	1,404	111				
		Average....	12.53	1.08	14.12	+0.51	0.077	0.896	1.332	0.359	—16	—10	0.77	36.8	1,380	...	..	26.9	3.6	
Thyroid (P. D.), 2 grains daily	4	7/23-8/9	13.56	1.17	13.59	—1.14	0.114	0.972	1.371	0.284	—12	— 8	0.79	38.1	1,423	110	66	....	...	2,400
		8/10-27	14.26	1.32	15.72	+0.14	0.135	1.285	1.522	0.102	— 9	— 2	0.79	40.2	1,502	110	66			
		Average....	13.91	1.24	14.65	—0.50	0.124	1.129	1.446	0.193	—10	— 5	0.79	39.1	1,462	...	..	14.2	—3.4	

* B refers to the Boothby surface area standard and T to the Talbot height standard.

"Oct. 1, 1938 (period 2): There is a 50 per cent collapse of the left lung. Stringlike adhesions from the apical region have prevented complete collapse. The areas of calcification are more distinctly seen.

"Feb. 24, 1939 (period 10): There has been slight reexpansion of the lower lobe of the left lung. No fluid is present. The lesion in the upper lobe seems to be more productive in type, and the calcifications are more discrete and seem denser.

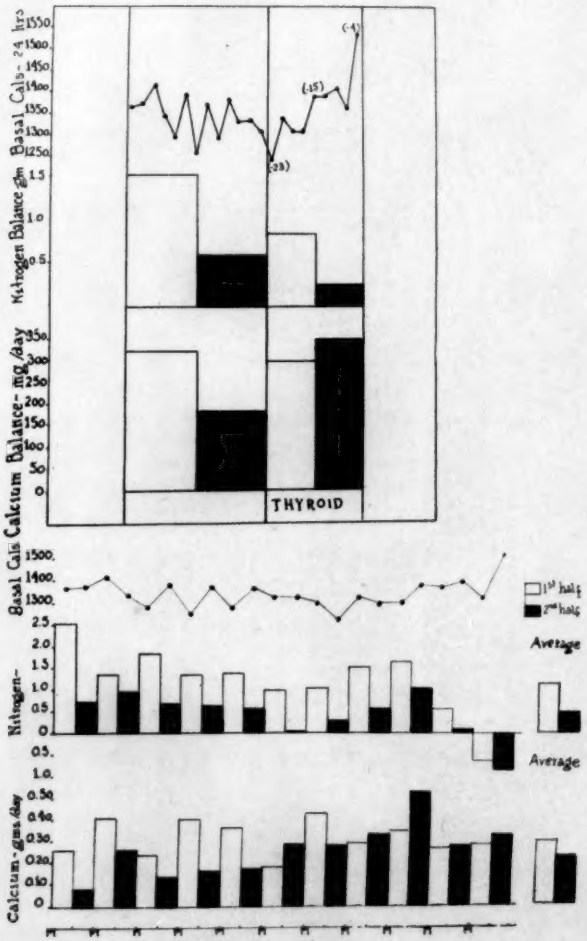

Chart 3.—Data for R. C. The retentions of calcium and nitrogen have been plotted for menstrual half-cycles. An average of the data for eleven cycles brings out the point that before the administration of thyroid the retention of calcium in the second half of the cycle was little more than half that in the first half and that after thyroid was given the retention in the second half was greater than that in the first half. The effect on nitrogen was to cause a further diminution in the retention, which was already less in the second half than in the first.

"Aug. 19, 1939 (period 20): The shadow of the left lung shows little change. The right lung shows a new infiltration, not previously seen, in the apical area and at the level of the first and second interspaces."

It was felt that improvement had occurred coincidentally with the increase in the retention of calcium but that spread of the disease process had followed the negative nitrogen balance. From a large number of long term balances my associates and I have concluded that healing is not to be expected when either the calcium or the nitrogen balance is negative, that usually the two balances parallel well and that recovery is characterized by high storage of both substances. This point is illustrated elsewhere [7] and will be developed further in the next paper in this series. Further, as will be seen from the chart, in which the data for the eighteen day periods are plotted as single bars, there is a rhythmic fluctuation which becomes definitely stabilized after the use of thyroid.

In the preceding paper in this series [8] the depressing effect of estrogen on the retention of calcium was demonstrated for 6 girls at puberty. Because this hormone seems to be operative largely during the second half of the menstrual cycle, it seemed worth while to plot retentions in menstrual half-cycles. When this was done for R. C. it appeared that the balances were significantly lower in the second half of the cycle than in the first and that the improvement following the administration of thyroid was referable to a change in the second half of the cycle. No determinations of estrogen were made, but the point is recorded here as one warranting confirmation by workers in the field of endocrinology and illustrating a possible antagonistic action between estrogen and thyroid.

COMMENT

While the desirability of rest with a large variety of medical conditions seems undisputed, over long periods certain undesirable concomitants of it are admitted and accepted as necessary evils. The observations reported suggest that in the period of lowered metabolism accompanying prolonged rest calcium retention might be specifically improved with small doses of thyroid, which, however, would have the undesirable effect of diminishing nitrogen retention. The effect on nitrogen retention, however, is readily offset by an increased intake of food, which, in turn, may be impossible without the stimulating effect of thyroid. Dosage is important. From these observations and those reported in the second article in this series it seems that to produce anabolic effects on children more than 1 grain of the Parke, Davis preparation is never required and that the effects of amounts greater than this would usually be catabolic.

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8. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: IV. Effect of Estrogen, Am. J. Dis. Child. **62**:708 (Oct.) 1941.

SUMMARY AND CONCLUSIONS

With a constant intake of food, thyroid administered in small doses to 2 children at prolonged rest in bed resulted in an increased retention of calcium; in larger doses retention was decreased. The amount of thyroid resulting in a maximal utilization of calcium reduced the retention of nitrogen. Total retentions of both items were increased by an increased intake of food, which was refused while metabolism was on a lower plane but taken well when metabolism was elevated by thyroid.

Dr. F. W. Hartman supervised the determinations of basal metabolism; Dr. O. H. Gaebler, the determinations of nitrogen and calcium balance, and Miss. E. Foster, the calculation of data relating to the diet.

PREVENTION OF DENTAL CARIES BY MASSIVE DOSES OF VITAMIN D

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Previous studies [1] have indicated that diet plays an important role in the causation and prevention of dental caries. Some investigators,[2] in attempting to determine the dietary factors which might be responsible for the occurrence of dental caries, stressed the significance of the vitamins A, C and D. We were particularly interested in the effect exerted by vitamin D; and since former studies had already indicated that a role was played by this vitamin, we decided to study the preventive effect of a single massive dose.

The treatment of rickets and tetany by single massive doses of vitamin D, first advocated by Vollmer,[3] has been extensively used in Europe by Harnapp,[4] Schirmer,[5] Braulke,[6] Bischoff,[7] Windorfer [8] and many other investigators. It has been shown that rickets and tetany can be

From the Division of Pediatrics of Sea View Hospital, Béla Schick, M.D., Director, and the Division of Oral Surgery, Ralph Howard Brodsky, D.M.D., Director.

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4. Harnapp, G. O.: Klin. Wchnschr. **15**:1043, 1936; **17**:390 and 391, 1938.

5. Schirmer, R.: Monatschr. f. Kinderh. **68**:269, 1936.

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8. Windorfer, A.: Klin. Wchnschr. **17**:228, 1938.

cured by oral or parenteral administration of a single dose of 600,000 international (U. S. P.) units of vitamin D and that the curative effect of this treatment is achieved more promptly than that obtained with the daily administration of small doses. Therefore it appeared possible that the administration of one massive dose of vitamin D might reduce the incidence of dental caries as well as or even more effectively than the daily administration of smaller doses.

MATERIAL AND METHODS

This study was carried out on a group of children admitted to the Sea View Hospital, the majority of whom suffered from active tuberculosis. The ages ranged from 2 to 16 years. A group of 200 was selected and divided into three subgroups of approximately equal distribution with regard to age, sex and general physical condition.

Group A consisted of 33 children who received the routine hospital diet, devoid of cod liver oil or any other additional source of vitamin D. This we considered our control group.

Distribution of the New Cavities Which Developed During the Period of Study

	Number of Children with							
	No Cavities	1 Cavity	2 Cavities	3 Cavities	4 Cavities	5 Cavities	Total Cavities	Average
Group A (33 children).....	15	7	4	5	1	1	39	1.18
Group B (33 children).....	27	2	2	1	1	0	13	0.39
Group C (35 children).....	29	6	0	0	0	0	6	0.17

Group B consisted of 33 children who received in addition to the routine hospital diet about 305,000 U. S. P. units of vitamin D in 30 cc. of a fish oil concentrate.[9] This was given in amounts of 1 or 2 teaspoons daily until the 30 cc. was administered. It contains vitamin D_3 (calciferol) as well as vitamin D_3 (activated 7-dehydrocholesterol) and includes appreciable quantities of vitamin A. No further vitamin D was added to the diet during the period of study.

Group C consisted of 35 children who received 600,000 U. S. P. units of vitamin D given orally in the form of crystalline vitamin D_2[10] in 1 cc. of oil in addition to the routine hospital diet. They, too, received no further addition of vitamin D to the diet during the period of study.

A comparison of the state of the oral hygiene before and at the conclusion of our study revealed about an equal distribution of mouths manifesting good, moderate and poor hygienic conditions in the three groups. Likewise, the incidence of caries and the number of deciduous and permanent teeth present at the time of the first examination were approximately equal for all groups.

All of the children received approximately the same daily diets, consisting of 1 quart (946 cc.) of milk, 5 to 10 ounces (142 to 284 Gm.) of meat or fish, 2 ounces (57 Gm.) of butter, 3 ounces (89 cc.) of fresh fruit juice plus 1 orange

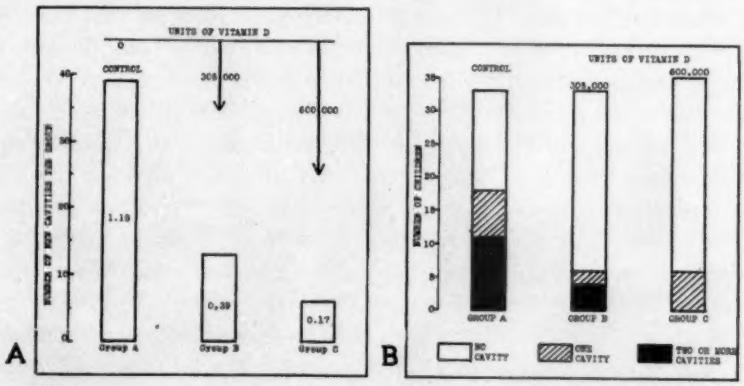
9. The preparation used was vi-delta liquid concentrate (Lederle Laboratories), which contains 90,000 U. S. P. units of vitamin A and 11,200 U. S. P. units of vitamin D per gram (per one and one-tenth cubic centimeters).

10. Calciferol (Burroughs, Wellcome & Co.) was the preparation used.

or apple, 3 ounces (85 Gm.) of cooked vegetable, 3 ounces of raw vegetable and 1 egg. In addition to this basic diet each child received such food as puddings or rhubarb, bread with each meal, cereals, cocoa and stewed fruits.

The children in the three groups lived under the same general conditions in the hospital and were subjected to the same environmental factors. All of them were regularly exposed to light and sun. Therefore the development of vitamin D deficiency in the control group was improbable and actually not demonstrable. There was no higher incidence of fever, symptoms of progression of the tuberculous process or incidental diseases in one group than in the others.

For each child a full series of roentgenograms of the teeth was made at the beginning of the study and at its end, eleven months later. The features relating to the conditions in the mouth were carefully charted and rechecked by two dentists after each roentgen examination, and the results were compared with the roentgen observations.[11] If a cavity became appreciably larger (recognizable on the roentgenograms) it was considered a new cavity in our tabulations. The



Charts illustrating the results of the study. *A* shows the number of new cavities which developed in each group during the period of study. The figures within the columns indicate the average number of cavities per child. *B*, indicates the number of children in whom no cavities, 1 cavity or 2 or more cavities developed.

data regarding the grouping of the children were not known to the examining dentists until all observations had been recorded, so that subjective factors could not influence the recording of cavities.

RESULTS

Although we started with a group of 200 children, our final tabulations include data for only 101. We felt that once a child left the hospital the resultant dietary and environmental changes could not permit his retention in our study.

A of the chart shows that in the control group 39 cavities, or 1.18 cavities per child, developed during the eleven month period of study;

11. The details of the method of charting have been described in a previous article.[12a]

in group B during the same period 13 cavities, or 0.39 cavity per child, developed, while in group C only 6 cavities, or 0.17 cavity per child, developed. *B* of the chart illustrates graphically the distribution of the cavities per child in the different groups.

COMMENT

The children of group B received about 2,455,000 units of vitamin A in addition to 305,000 units of vitamin D. Nevertheless about twice as many cavities developed in group B as in the children of group C, who received double the amount of vitamin D, without vitamin A. This seems to indicate that a single massive dose of vitamin A could not compensate for the smaller amount of vitamin D administered to group B as compared with group C and that vitamin D alone is the factor influencing quantitatively the development of caries. Morever, the optimum requirement of vitamin D for the maintenance of a normal calcium-phosphorus metabolism in a growing child seems not to coincide with its optimum requirement for the prevention of dental caries. However, the mechanism of the effect of massive doses of vitamin D is not understood. Chemical analyses of the teeth, as well as chemical and bacteriologic investigation of the oral cavity before and after the administration of massive doses of vitamin D, might be desirable.

The incidence of caries prior to our study in all of the groups was relatively high, averaging approximately 4 cavities per child. Comparison of this incidence with our final results, including those for the control group, indicates that a well balanced hospital diet without any additional supply of vitamin D plays a role in the control of dental caries. This has been demonstrated in previous studies.[12] The addition of a massive dose of vitamin D seems to bring the incidence of new cavities close to the zero point.

None of the children who had received a single massive dose of vitamin D showed any toxic manifestation. Repeated examinations of the urine did not reveal any calcium-containing casts. The administration of a single massive dose of vitamin D appears to be safe, an observation which has been considered in detail by Vollmer.[3]

Further studies are necessary to determine the duration of the protection achieved by the administration of a single dose of 600,000 units of vitamin D. In view of the experience derived from rickets prophylaxis, in which single massive doses of vitamin D have been used, it may be expected that two or three massive doses per year will be required for optimum dental caries prophylaxis.

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12. (*a*) Brodsky, R. H.: J. Am. Dent. A. **20**:1440 (Aug.) 1933. (*b*) Schoenthal, L., and Brodsky, R. H.: Dietary Control and Etiology of Dental Caries, Am. J. Dis. Child. **46**:91 (July) 1933. (*c*) Boyd, J. D.; Drain, C. L., and Nelson, M. V.: Dietary Control and Dental Caries, ibid. **38**:721 (Oct.) 1929.

The incidence of caries and gingival lesions seems to be the same for tuberculous and for nontuberculous children.[13]

CONCLUSIONS

A group of 200 children (for 101 of whom data are reported in this paper) who had tuberculosis or had been in contact with a patient with the disease were studied carefully for a period of approximately one year in the Sea View Hospital to determine the effect of a single massive dose of vitamin D on the incidence of dental caries. These children were divided into three groups: a control group (A), who received only the hospital diet, devoid of cod liver oil or any other additional source of vitamin D; a second group (B), who received, in addition to the hospital diet, 305,000 U. S. P. units of vitamin D and 2,455,000 U. S. P. units of vitamin A in 30 cc. of fish liver oil concentrate, and a third group (C), who received 600,000 U. S. P. units of vitamin D in the form of crystalline vitamin D_2 in 1 cc. of oil in addition to the same hospital diet.

In the control group (A) there developed 39 cavities, or 1.18 new cavities per child, during the observation period. In group B there developed 13 cavities, or 0.39 cavity per child, and in group C there developed 6 cavities, or 0.17 cavity per child.

None of the children showed any toxic manifestation after the administration of the single massive dose of vitamin D.

Further studies are required, on larger groups. However, the results of this study seem to indicate that the incidence of dental caries may be markedly decreased by the administration of a single massive dose of vitamin D.

14 East Eighty-First Street.

17 East Eighty-Fourth Street.

25 Central Park West.

13. This statement is based on a comparison of the observations on these children with unpublished data for a group of 1,000 normal children who were studied by Dr. Brodsky.

HEMATOLOGIC STANDARDS FOR HEALTHY NEWBORN INFANTS

ERYTHROCYTE COUNT, HEMOGLOBIN CONTENT, CELL VOLUME, COLOR INDEX, VOLUME INDEX AND SATURATION INDEX

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This is one of a series of articles which give hematologic standards for normal persons from birth through adult life.[1] Although there is an

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From the Department of Medicine, University of Oregon Medical School.

1. (*a*) Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards: Redeterminations Based on Findings in One Hundred and Thirty-Seven Healthy Young Men, Arch. Int. Med. **37**:685-706 (May) 1926. (*b*) Osgood, E. E., and Haskins, H. D.: The Relation Between Cell Count, Cell Volume and Hemoglobin Content of the Venous Blood of Normal Young Women: Redeterminations of Color Index, Volume Index and Saturation Index Standards Based on Observations in One Hundred Cases, ibid. **39**:643-655 (May) 1927. (*c*) Osgood, E. E., and Baker, R. L.: Erythrocyte, Hemoglobin, Cell Volume and Color, Volume and Saturation Index Standards for Normal Children of School Age, Am. J. Dis. Child. **50**:343-358 (Aug.) 1935. (*d*) Osgood, E. E.: Normal Hematologic Standards, Arch. Int. Med. **56**:849-863 (Nov.) 1935. (*e*) Osgood, E. E., and others: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Children Four to Seven Years of Age, Am. J. Dis. Child. **58**:61-70 (July) 1939; (*f*) Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children: Standards for Children Eight to Fourteen Years of Age, ibid. **58**:282-294 (Aug.) 1939; (*g*) Total Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Adolescents Fifteen to Eighteen Years of Age, J. Lab. & Clin. Med. **24**:905-912 (June) 1939; (*h*) Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates, Determined for Healthy Persons Nineteen Years of Age and Over, Arch. Int. Med. **64**:105-120 (July) 1939. (*i*) Chuinard, E. G.; Osgood, E. E., and Ellis, D. M.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Newborn Infants, to be published. (*j*) Osgood, E. E., and others: Erythrocyte Counts, Hemoglobin, Cell Volume, and Color, Volume and Saturation Index Standards for Healthy Adolescent Males, Fifteen Years of Age and Over, to be published; (*k*) Erythrocyte Counts, Hemoglobin, Cell Volume, and Color, Volume and Saturation Index Standards for Healthy Females, Fifteen Years of Age and Over, to be published; (*l*) Reticulocyte Counts

(Footnote continued on next page)

extensive literature [2] (table 1) dealing with normal hematologic data for the newborn period, the extreme variations in the accuracy of the methods used and in the results obtained show the need for further data.

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in Healthy Newborn Infants, to be published; (*m*) Icterus Index Determinations in Healthy Newborn Infants, to be published; (*n*) Reticulocyte Counts in Healthy Adolescent Boys and Girls, to be published.

2. (*a*) Lucas, W. P., and Dearing, B. F.: Blood Volume in Infants Estimated by the Vital Dye Method, Am. J. Dis. Child. **21**:96-106 (Jan.) 1921. (*b*) Lucas, W. P.; Dearing, B. F.; Hoobler, H. R.; Cox, A.; Jones, M. R., and Smyth, F. S.: Blood Studies in the New-Born: Morphological, Chemical, Coagulation, Urobilin and Bilirubin, ibid. **22**:525-559 (Dec.) 1921. (*c*) Lippman, H. S.: A Morphologic Quantitative Study of the Blood Corpuscles in the New-Born Period, ibid. **27**:473-526 (May) 1924. (*d*) Haden, R. L., and Neff, F. C.: The Volume Index and Color Index of the Red Blood Corpuscles in New-Born Infants, ibid. **28**:458-463 (Oct.) 1924. (*e*) Börner, R.: Das Blut des Menschen, mit neueren Methoden untersucht: III. Das Blut des Neugeborenen in bezug auf absoluten Hämaglobingehalt, Erythrocytenzahl, Gehalt eines Erythrocyten und Hämoglobin, Hämoglobin pro μ^2 Oberfläche des Erythrocyten und Brechungsexponent bzw. Eiweissprozente des Plasmas, Arch. f. d. ges. Physiol. **220**:716-737, 1928. (*f*) Allumbaugh, H. R.: A Study of the Blood of the Mother and New Born, Proc. Soc. Exper. Biol. & Med. **26**:814-816 (June) 1929. (*g*) Forkner, C. E.: Studies on the Living Blood Cells of the Newborn, Bull. Johns Hopkins Hosp. **45**:75-94 (Aug.) 1929. (*h*) Mitchell, J. M.: Relationship of Jaundice and Weight to Blood Values in the New-Born Infant, Am. J. Dis. Child. **38**:518-525 (Sept.) 1929. (*i*) Mackay, H. M. M.: The Normal Hemoglobin Level During the First Year of Life: Revised Figures, Arch. Dis. Childhood **8**:221-225 (June) 1933. (*j*) Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life: I. Normal Values for Erythrocytes, Hemoglobin, Reticulocytes and Platelets, and Their Relationship to Neonatal Bleeding and Coagulation Time, Am. J. Dis. Child. **46**:990-1010 (Nov.) 1933. (*k*) Kato, K., and Emery, O. J.: Hemoglobin Content of the Blood in Infancy: A Study of Seven Hundred and Eighty Cases from Birth to Two Years, with One Thousand and Sixty-Five Determinations, Folia haemat. **49**:106-114 (Jan.) 1933. (*l*) Dhar, J.: Haematological Studies of Fifty New-Born, Indian J. Pediat. **1**:249-267 (July) 1934. (*m*) Martin, L. C., and Evans, S. M.: Blood Counts of Newborn Infants in Relation to Icterus Neonatorum, Arch. Dis. Childhood **10**:355-362 (Oct.) 1935. (*n*) Rosenbloom, D.: Platelet and Blood-Cell Counts in Newborn During the First Two Days of Life, Proc. Soc. Exper. Biol. & Med. **32**:906-908 (March) 1935. (*o*) Whitby, L. E. H., and Hynes, M.: The Quantitative Estimation of the Fragility of the Red Corpuscles, J. Path. & Bact. **40**:219-230 (March) 1935. (*p*) Guest, G. M., and Brown, E. W.: Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood: I. Size and Hemoglobin Content of the Erythrocytes in Nutritional Anemia, Am. J. Dis. Child. **52**:616-626 (Sept.) 1936. (*q*) Mugrage, E. R., and Andresen, M. I.: Values for Red Cells of Average Infants and Children, ibid. **51**:775-791 (April) 1936. (*r*) Andersen, B., and Ortmann, G.: On the Number of Erythrocytes and the Content of Haemoglobin in the Blood of New-Born Children, Acta med. Scandinav. **93**:410-419, 1937. (*s*) Faxén, R.: Red Blood Picture in Healthy Infants, Acta pædiat. (supp. 1)

(Footnote continued on next page)

TABLE 1.—*Hematologic Standards for Newborn Infants Reported in the Literature Since 1921* *

Author ‡	Red Blood Cells, Millions per Cu. Mm.		Method of Hemoglobin Determination	Hemoglobin Content				Hemoglobin Coefficient	Color Index	Cell Volume, Cc. per 100 Cc.		Volume Coefficient	Volume Index	Saturation Index	Age of Infant	Number of Determinations
				Percentage		Gm. per 100 Cc.										
	Average	Range		Average	Range	Average	Range			Average	Range					
Lucas and Dearing [2a]	5.47	4.65-7.20	.....	105.8	75-135	14.60	10.35-18.63	13.32	0.75	58.39	46.3-70.5	53.37	1.12	0.67	1-10 days	Hemoglobin 25 Erythrocytes 17 Cell volume 28
Lucas, Dearing, Hoobler, Cox, Jones and Smyth [2b]	5.07	.....	Robscheit	110.1	91-117	15.19	12.56-16.15	14.98	0.84	.....	.....	.....	....	....	1-10 days	Hemoglobin 211 Erythrocytes 202
Lippman [2c]	5.42	3.68-7.00	.....	.....	.....	.....	.....	.....	....	.....	.....	.....	....	....	1-48 hours	235
Haden and Neff [2d]	4.06	3.52-4.57	.....	113.0	100-129	17.70	15.6 -20.1	21.69	1.22	57.6	52.0-66.5	70.59	1.48	0.82	11 hours to 9 days	9
Börner [2e]	5.18	4.14-6.01†	Bürker	145.0	117-171.7†	20.01	16.19-23.71†	19.04	1.07	.....	.....	.....	....	....	25 minutes to 10 days	26†
	4.44	4.25-4.89‡		126.2	113-138.8‡	17.42	15.59-19.16‡	19.62	1.10	.....	.....	.....	....	....	12 hours to 3½ days	4‡
Allumbaugh [2f]	5.52	4.45-6.52	.....	122.1	102-144	16.85	14.08-19.87	15.26	0.98	.....	.....	.....	....	....	Newborn	50
Forkner [2g]	5.63	4.34-6.99	Sahli	144.8	105-190.5	19.98	14.49-26.20	17.74	0.99	.....	.....	.....	....	....	1-10 days	Hemoglobin 39 Erythrocytes 40
Mitchell [2h]	5.28	3.26-8.23	Sahli	113.3	74-154	15.63	10.21-21.26	14.80	0.83	57.74	34.0-79.0	54.68	1.15	0.72	1-10 days	276 Cell volume 200
Mackay [2i]	....	.....	Price-Jones	145.7	.....	20.11	.....	.....	....	.....	.....	.....	....	....	Under 24 hours	62
Merritt and Davidson [2j]	5.95	4.60-6.80	Wong	169.6	123.2-199.3	23.40	17.0 -27.5	19.66	1.10	.....	.....	.....	....	....	1 day	73
Kato and Emery [2k]	....	.....	Newcomer	131.8	85.5-175.4	18.2	24.2 -11.8	.....	....	.....	.....	.....	....	....	1-96 hours	230
Dhar [2l]	5.08	4.00-6.34	Sahli	137.6	112-165.7	18.98	15.48-22.87	18.68	1.05	.....	.....	.....	....	....	Birth to 24 hours	50
Martin and Evans [2m]	5.26	.....	Haldane	118.0	.....	16.28	.....	14.77	0.87	.....	.....	.....	....	....	1-5 days	Hemoglobin 20 Erythrocytes 100

Rosenbloom [2n]	6.44	.....	Dare	116.8	.....	16.12	.....	12.52	0.70	.....	.....	.....	....	....	0-24 hours	117
Whitby and Hynes [2o]	7.00	5.90-7.69	Haldane	151.0	130-162	20.84	17.94-22.36	14.88	0.83	.....	.....	.....	....	....	Birth to 20 hours	10
Guest and Brown [2p]	4.77	4.02-5.93	Palmer carbon monoxide hemoglobin	128.3	94.9-159.4	17.70	13.10-22.00	18.58	1.04	52.7	69.1-42.9	55.4	1.16	0.90	Birth	8
Mugrage and Andresen [2q]	4.86	.....	Van Slyke and Osgood-Haskins	124.2	.....	17.14	.....	17.63	0.99	53.18	.....	54.71	1.15	0.86	Birth	40
Andersen and Ortmann [2r]	5.21	4.07-6.85	.....	126.4	92.0-179.9	17.44	12.70-24.84	16.80	0.94	56.5	42.0-78.5	54.1	1.14	0.82	1-24 hours	Hemoglobin 33 Erythrocytes 43 Cell volume 38
Faxén [2s]	5.44	.....	.....	164.3	.....	22.68	.....	21.29	1.19	.....	.....	.....	....	....	1-7 days	Hemoglobin 143 Erythrocytes 161 Hemoglobin coefficient 142
Hurwitz, Mulay and Lazarus [2t]	5.27	.....	Sahli	113.3	.....	15.84	.....	15.18	0.84	60.48	.....	57.97	1.23	0.68	1-10 days	101
Guest, Brown and Wing [2u]	4.8	.....	.....	129.7	.....	17.7	.....	18.80	1.05	.....	.....	.....	....	....	Birth	34†
	5.2	.....	.....	137.7	.....	19.0	.....	18.40	1.03	.....	.....	.....	....	....	1-10 days	80‡
Rasi and Bolletti [2v]	5.82	4.75-7.49	Sahli	115.0	95-158	19.90	16.44-27.33	17.10	0.96	.....	.....	.....	....	....	1 hour to 10 days	Hemoglobin 11 Erythrocytes 16
de San Martin [2w]	5.79	4.96-7.65	Iron content of blood and Hellige-Sahli	141.6	108-198	19.54	14.92-27.28	16.87	0.95	48.26	40.0-60.0	41.68	0.88	1.08	3-23 hours	35
Gallerani [2x]	5.50	4.56-7.34	.....	.....	.....	.....	.....	.....	....	.....	.....	.....	....	....	To 24 hours	52
Waugh, Merchant and Maughan [2y]	....	.....	Photoelectric colorimeter	110.3	.....	15.21	.....	.....	....	48.63	.....	.....	....	....	1-9 days	Hemoglobin 221 Cell volume 220
Phillips [2z]	6.06†	.....	Osgood-Haskins	140.0	125-159†	19.3	17.2 -21.9	15.92	0.89	.....	.....	.....	....	....	20-30 hours	33†
	4.90‡	.....		113.0	89-131‡	15.6	12.3 -18.1	15.92	0.89	.....	.....	.....	....	....	20-30 hours	Hemoglobin 37‡ Erythrocytes 38‡

* Lippman [2c] reviewed the earlier literature.
† Cord tied late.
‡ Cord tied early.

SUBJECTS

The 195 subjects were white, full term infants born at the Multnomah County Hospital, Portland, Ore., in whom no evidence of disease was found by physical examination. Since this is a county hospital, all of the infants were from families with a low income level, and the mothers had resided for at least six months in Multnomah County, at or near sea level. Serologic tests for syphilis on the cord blood gave negative results for all infants. Approximately 10 infants of each sex were studied on each day of life for the first ten days. To avoid multiple fontanel punctures each set of determinations was made on a different infant.

METHODS

With aseptic precautions 10 cc. of blood was obtained from the fontanel and introduced at once into a test tube containing 20 mg. of potassium oxalate.[3] The red cell counts reported are the averages of two separate counts made by the technic described elsewhere.[4] The Osgood-Haskins method[5] of determining the hemoglobin content was used; it has been shown to give results which have an error of less than ± 5 per cent. The cell volume was determined by centrifuging to constant volume[6] and has not been corrected for shrinkage due to the oxalate. The hemoglobin and volume coefficients were calculated from these data.[7] The color, volume and saturation indexes were calculated from the average hemoglobin and volume coefficients for the entire series. The indexes given in table 1 were all calculated from the authors' data on the basis of these standards so that they would be comparable.

19:1-142, 1937. (*t*) Hurwitz, S.; Mulay, A. S., and Lazarus, D. S.: Sedimentation Time and Other Blood Factors in the Newborn Infant, J. Pediat. **12**:785-788 (June) 1938. (*u*) Guest, G. M.; Brown, E. W., and Wing, M.: Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood: II. Variability in Number, Size and Hemoglobin Content of the Erythrocytes During the First Five Years of Life, Am. J. Dis. Child. **56**:529-549 (Sept.) 1938. (*v*) Rasi, F., and Bolletti, M.: Formula eritrocitometrica, numero dei globuli rossi e dei reticolociti nel neonato e loro variazioni nei primi giorni di vita, Riv. di clin. pediat. **36**:605-638 (July) 1938. (*w*) de San Martin, A. M.: Determinación de la hemoglobina, hierro, globulos rojos y volumen globular en el recien nacido normal y en el prematuro, dentro de las 24 horas, Arch. argent. de pediat. **9**:63-72 (July) 1938. (*x*) Gallerani, U.: Il numero dei globuli rossi e le resistenze globulari nei primi giorni di vita con particolare riguardo all'ittero dei neonati, Lattante **9**:488-505 (Nov.); 529-550 (Dec.) 1938. (*y*) Waugh, T. R.; Merchant, F. T., and Maughan, G. B.: Blood Studies on the Newborn: I. Determination of Hemoglobin, Volume of Packed Red Cells, Reticulocytes, and Fragility of the Erythrocytes over a Nine-Day Period, Am. J. M. Sc. **198**:646-665 (Nov.) 1939. (*z*) Phillips, B. I.: Personal communication to the authors. (*a'*) DeMarsh, Q. B.; Alt, H. L., and Windle, W. F.: The Effect of Depriving the Infant of Its Placental Blood: On the Blood Picture During the First Week of Life, J. A. M. A. **116**:2568-2573 (June 7) 1941.

3. Osgood, E. E.: A Textbook of Laboratory Diagnosis, ed. 3, Philadelphia, The Blakiston Company, 1940, pp. 458-461.
4. Osgood,[3] pp. 471-475.
5. Osgood,[3] pp. 463-469.
6. Osgood,[3] pp. 487-488.
7. Osgood,[3] pp. 179-183.

The total, differential and absolute leukocyte counts, the sedimentation rates, the reticulocyte counts and the icterus indexes were determined on the same blood samples and will be reported elsewhere.[8]

The percentages of hemoglobin in table 1 were all recalculated from the authors' data on the basis of 13.8 Gm. per hundred cubic centimeters as 100 per cent for purposes of comparison.

TABLE 2.—*Summary of Hematologic Data for Healthy Infants One to Ten Days of Age*

Age Days	Number of Subjects	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin Content: Percentage	Hemoglobin Content: Gm. per 100 Cc.	Hemoglobin Coefficient	Color Index	Cell Volume	Volume Coefficient	Volume Index	Saturation Index
Boys										
1	11	4.66	126.0	17.39	18.67	1.05	46.09	49.51	1.04	1.01
2	10	4.52	123.2	16.99	18.90	1.06	43.80	48.59	1.02	1.04
3	10	4.73	129.7	17.84	18.94	1.06	46.80	49.78	1.05	1.02
4	9	4.78	118.8	16.39	17.30	0.97	43.27	45.44	0.95	1.02
5	10	4.57	112.6	15.54	17.21	0.97	41.58	45.68	0.96	1.00
6	10	4.81	118.1	16.30	17.00	0.95	44.09	46.00	0.97	1.00
7	9	4.56	123.3	17.01	18.59	1.04	44.05	48.50	1.02	1.04
8	10	4.46	108.7	15.00	16.94	0.95	39.42	44.60	0.94	1.02
9	11	4.83	115.3	15.91	16.49	0.92	42.54	44.02	0.92	1.00
10	9	4.27	115.8	15.97	18.82	1.06	40.96	48.35	1.01	1.05
Total.....	99									
Average.....		4.63	119.2	16.44	17.87	1.00	43.30	47.08	0.99	1.02
Maximum....		6.32	163.8	22.62	22.35	1.25	61.08	61.34	1.29	1.46
Minimum.....		2.65	75.1	10.36	12.52	0.70	25.50	33.88	0.71	0.81
Girls										
1	9	4.65	123.3	17.01	18.44	1.03	45.00	49.68	1.04	0.99
2	10	4.71	127.4	17.58	18.64	1.04	46.54	49.32	1.04	1.01
3	10	4.95	125.2	17.28	17.52	0.98	48.80	49.38	1.04	0.95
4	10	4.56	126.4	17.45	19.08	1.07	44.78	49.01	1.03	1.04
5	8	4.56	111.5	15.39	16.96	0.95	42.40	46.88	0.98	0.97
6	10	4.53	115.8	15.99	17.86	1.00	43.46	48.44	1.02	0.98
7	10	4.07	102.2	14.10	17.60	0.99	38.92	48.55	1.02	0.97
8	10	4.52	116.1	16.02	17.75	1.00	44.13	48.94	1.03	0.97
9	9	4.58	112.2	15.48	16.95	0.95	40.64	44.28	0.93	1.03
10	10	4.28	107.8	14.88	17.44	0.98	39.46	46.19	0.97	1.01
Total.....	96									
Average.....		4.54	116.9	16.13	17.84	1.00	43.50	48.12	1.01	0.99
Maximum....		5.71	160.4	22.12	23.52	1.32	60.00	60.61	1.27	1.26
Minimum.....		3.17	74.6	10.29	13.26	0.74	28.05	36.15	0.76	0.77
Boys and Girls										
Total.....	195									
Average.....		4.58	118.0	16.29	17.85	1.00	43.40	47.56	1.00	1.01
Maximum....		6.32	163.8	22.62	23.52	1.32	61.08	61.34	1.29	1.46
Minimum.....		2.65	74.6	10.29	12.52	0.70	25.50	33.88	0.71	0.77

RESULTS

Table 2 summarizes the average results at each age level (by days) for boys and for girls and gives the average, maximum and minimum values for the entire series.

Note that there is little variation in the average values for any of these determinations with either age or sex during this age period.

8. Chuinard, Osgood and Ellis.[11] Osgood and others (footnote 1 *l* and *m*).

although there is a slight tendency for the hemoglobin content and the red blood cell count to decrease. These differences do not seem great enough to justify separate standards for each day. The frequency distributions of the results are shown in charts 1 and 2. The values are all within the range of those previously reported but tend to be lower than the majority (table 1). The explanation of this is probably to be found in the data of Börner,[2e] Phillips [2z] and DeMarsh and co-workers,[2a']

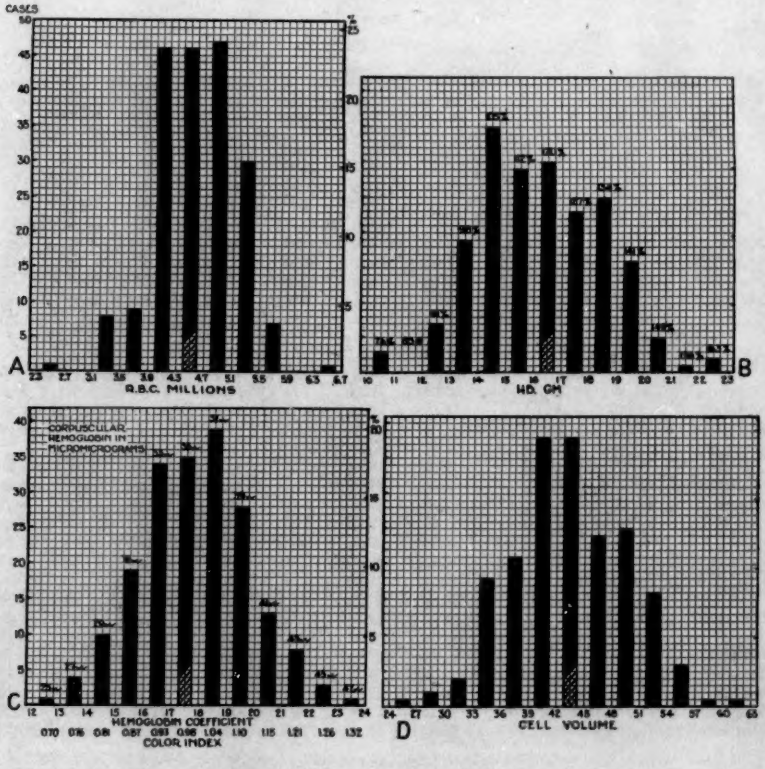

Chart 1.—Frequency distributions of values for, *A*, red blood cell count; *B*, hemoglobin content (expressed in percentages and in grams per hundred cubic centimeters of blood); *C*, hemoglobin coefficient, color index and mean corpuscular hemoglobin, and, *D*, cell volume (expressed in cubic centimeters of packed red cells per hundred cubic centimeters of blood).

all of whom showed that if the cord is tied early, as was done in the case of all our subjects, the red blood cell count and the hemoglobin content are significantly lower than if time is allowed for expression of blood from the placenta before the cord is tied. Variations in the time of tying the cord probably account in part for the extreme variability of the normal values for this age period reported by different investigators

(table 1). This will not account, however, for the variations in the hemoglobin and volume coefficients. The variations in the former are probably due largely to wide variations in the accuracy of the methods used for determining the hemoglobin content and in the latter to failure of many workers to centrifuge their samples of blood to constant volume.

Comparison of the average hemoglobin coefficient of 17.8 with the averages for other age groups, namely, 12 for children 4 to 13 years of age, 14.3 for women 14 to 30 years of age and 14.7 for men 14 to 30 years of age, shows that newborn infants have a significantly higher hemoglobin concentration in the red cells than older persons. From a comparison of the volume coefficient of 47.6 with the corresponding values of 36 for children 4 to 17 years of age, 43 for women 18 to 30 years of age and 41 for men 18 to 30 years of age it is evident that the

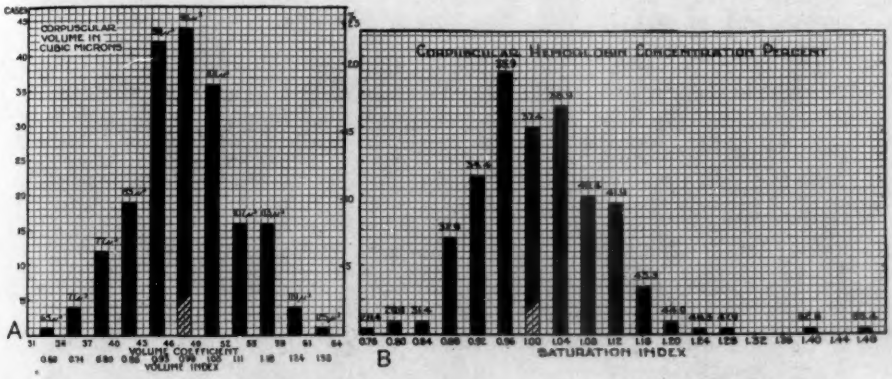

Chart 2.—Frequency distribution of values for, *A*, volume coefficient, volume index and mean corpuscular volume, and, *B*, saturation index and mean corpuscular hemoglobin concentration.

erythrocytes of newborn infants are significantly larger than those of older persons. Standards for other age groups will, therefore, not be satisfactory for calculating color, volume and saturation indexes for infants. It is also evident that it is futile to try to pick as ideal any one number of grams of hemoglobin per hundred cubic centimeters of blood to serve as 100 per cent in calculating percentages of hemoglobin concentration. The only solution appears to be to report the hemoglobin content in terms of grams per hundred cubic centimeters of blood and to calculate the indexes from the average normal coefficients for persons of the same sex and age group.

The corpuscular hemoglobin expressed in micromicrograms is given in chart 1 *C*, or it may be calculated from the hemoglobin coefficient by multiplying by 2. Corpuscular volume in cubic microns is given in

chart 2 *A*, or it may be calculated from the volume coefficient by multiplying by 2. The corpuscular hemoglobin concentration is given in chart 2 *B*, or it may be calculated from the data in the tables from the formula $\frac{\text{hemoglobin coefficient}}{\text{volume coefficient}} \times 100$. The average value of 37 per cent for the corpuscular hemoglobin concentration does not differ significantly from the value of 36 for adult males.

SUMMARY

The erythrocyte count, the hemoglobin content, the cell volume and the color, volume and saturation indexes have been determined on oxalated fontanel blood of 195 infants, about 10 of each sex being studied on each of the first ten days of life. No significant differences with age or sex were noted during this age period.

The average erythrocyte count was 4,600,000 cells per cubic millimeter, with an extreme range from 2,600,000 to 6,300,000; 95 per cent of the values fell in the range from 3,400,000 to 5,800,000.

The average hemoglobin concentration was 16.3 Gm. per hundred cubic centimeters, with an extreme range from 10.3 to 22.6 Gm.; 95 per cent of the values fell in the range from 12.3 to 20.3 Gm.

The average packed red cell volume was 43.4 cc. per hundred cubic centimeters of blood, with an extreme range from 25.5 to 61.0 cc.; 95 per cent of the values fell in the range from 31.5 to 55.5 cc.

The average hemoglobin coefficient was 17.8, with an extreme range from 12.5 to 23.5; 95 per cent of the values fell in the range from 14 to 22. These results correspond to an average color index of 1.00, with a range from 0.78 to 1.23.

The average volume coefficient was 47.6, with an extreme range from 34 to 61; 95 per cent of the values fell in the range from 37 to 58, which corresponds to a volume index range of 0.79 to 1.2.

The average saturation index was 1.00, with an extreme range from 0.77 to 1.46; 95 per cent of the values fell in the range from 0.85 to 1.15.

The cells of newborn infants are larger and contain more hemoglobin than those of older persons, but the corpuscular hemoglobin concentration is similar to that of adult men.

Hemoglobin content should be reported in terms of grams per hundred cubic centimeters of blood; for the calculation of color, volume and saturation indexes, standards for healthy persons of the patient's sex and age group must be used.

THE TUBERCULIN TEST

COMPARATIVE RESULTS OF THE INTRADERMAL AND THE PATCH TEST FOR ONE THOUSAND PATIENTS

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AND
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FLUSHING, N. Y.

It was shown by Moro [1] in 1908 that if an ointment composed of equal parts of tuberculin and hydrous wool fat is rubbed into the skin of a susceptible subject a specific local inflammatory reaction will appear. In the same year Lautier [2] introduced a similar test, consisting of applying diluted old tuberculin to the skin and then covering it with cotton. Wegerer [3] (1913) improved on this method by rubbing tuberculin into the skin, after which it was protected by adhesive tape. A similar test, which required no friction, was described by Blumenau [4] in 1914. Habetin [5] (1928) introduced the use of an ointment containing old tuberculin. Lovett [6] in 1929 proved that rubbing the skin over the sternum with ether removed much of the oil from the pores and made the test more efficient. Hille [7] (1929) advocated this procedure and claimed to have obtained 30 per cent more positive reactions by this method. In 1931 Malmberg and Fromm [8] mixed tuberculin with adhe-

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1. Moro, E.: Ueber eine diagnostische verwertbare Reaktion der Haut auf Einreibung mit Tuberkulin salbe, München. med. Wchnschr. **55**:216, 1908.

2. Lautier, R.: Nouveau procídé de cuti-réaction à la tuberculine chez l'homme, Compt. rend. Soc. de biol. **64**:5 and 91 (Jan. 7) 1908.

3. Wegerer, F.: Studien über Tuberkulin-Perkutanreaktionen, Med. Klin. **9**: 575, 1913.

4. Blumenau, N.: Ueber du Moro-Doganoffsche Reaktion und über eine neue Tropfenpflasterreaktion, Ztschr. f. Tuberk. **22**:157, 1914.

5. Habetin, P.: Die Tuberkulinsalbenpflasterprobe, Wien. klin. Wchnschr. **41**:703 (May 17) 1928.

6. Lovett, B. R.: Percutaneous Tuberculin Reaction, Am. J. Dis. Child. **37**: 918 (May) 1929.

7. Hille, K.: Zur Technik der perkutanen Tuberkulinreaktion nach Moro, Arch. f. Kinderh. **88**:14 (July 12) 1929.

8. Malmberg, N., and Fromm, B.: New Tuberculin Test, Acta pædiat. **10**: 435, 1931.

sive plaster so that 1 square cm. of the latter contained 1 drop of the testing material.

In this country the name tuberculin patch test was given by one of us [9] (M. G.) to a method of testing for tuberculosis by the application of tuberculin and adhesive plaster to the intact skin, which if the reaction is positive results in an inflammatory area of reaction studded with small confluent papules and vesicles (fig. 1 *A*).

The advantages pointed out for this test were as follows:

1. It is painless and therefore does not frighten the child or spoil the good relationship between physician and patient. This is especially important in testing a resisting child.

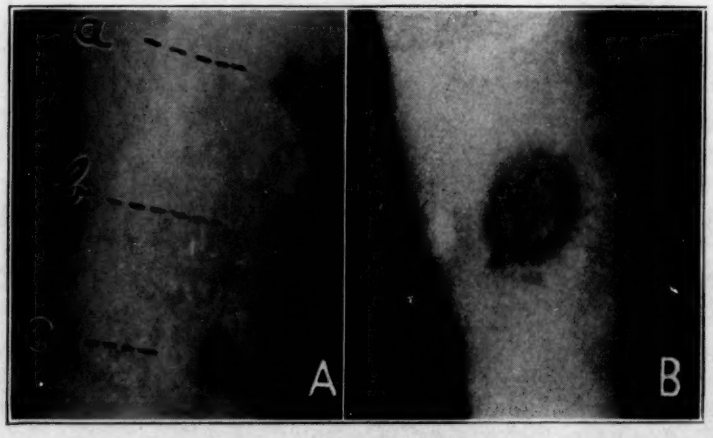

Fig. 1.—Results of tuberculin tests. *A*, results of patch test, showing *a* and *c*, positive reaction, and *b*, control. *B*, strongly positive reaction, with necrosis and vesiculation, to a Mantoux test with 0.1 mg. of a 1:1,000 dilution of old tuberculin.

2. It requires no boring, puncturing, scratching or rubbing of the skin.

3. It does not necessitate the use of syringes and needles (as in the Mantoux [10] test) or of lancets or borers (as in the Pirquet [11] test).

4. There are no instruments to sterilize.

5. There is no danger of infection.

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9. Grozin, M.: The Tuberculin Patch Test: A Diagnostic Aid in Tuberculosis, Am. J. Dis. Child. **46**:17 (July) 1933.

10. Mantoux, C.: Intra-dermo-reaction de la tuberculine, Compt. rend. Acad. d. sc. **147**:355, 1908.

11. von Pirquet, C.: Tuberculindiagnose durch kutane Impfung, Berl. klin. Wchnschr. **20**:22, 1907.

6. There is considerably less risk attached to this test than to the intradermal method, which may give rise to necrosis, vesiculation and ulceration, especially in Negro children [12] (fig. 1 *B*).

7. There is no fear of a general or focal reaction.

8. The technic is simple and is therefore especially adapted to use by those who are not accustomed to making intracutaneous tests.

9. It saves time, particularly when large numbers of children are to be tested.

10. It is possible to control the size of the area of reaction, since it is limited to the surface covered by the adhesive tape.

The recognition of these advantages has in recent years led to development of commercial materials for performing tuberculin patch tests, as well as to publication of a vast amount of literature on this subject. Waring,[13] comparing the results of this test with those of the Mantoux test done with 0.1 mg. of old tuberculin, found them to run nearly parallel when the reaction to the latter test was definitely positive, although there was some disagreement in those cases in which the reaction to the intradermal test was only slightly positive (1 +). According to Ando,[14] the tuberculin patch test compared favorably with the Mantoux and Pirquet tests. Similar conclusions were reached by Hiro.[15] Anzén [16] found the patch test somewhat less reliable for work with older children. Hart [17] in testing 536 patients found that 100 had a positive reaction to the Mantoux test and of these 97 had a positive reaction to the tuberculin patch test. Steward [18] observed conformity in the results of the two tests in 93.75 per cent of cases. Brown,[19] while confirming the specificity of the tuberculin patch test, found it to be less sensitive than the intradermal method. Court [20] observed no

12. Gleich, M.: Comparative Value of von Pirquet and Mantoux Tests in Colored Infants and Children, Arch. Pediat. **49**:399 (June) 1932.

13. Waring, J. L.: The Tuberculin Patch Test, J. Pediat. **6**:202 (Feb.) 1935.

14. Ando, K.: The Tuberculin Patch Test, Acta pædiat. japon. **41**:1300, 1935.

15. Hiro, Y., and Takahashi, S.: Vergleichende Untersuchungen über die Pirquetsche Reaktion und die Tuberkulinheftpflasterprobe, Monatschr. f. Kinderh. **70**:381, 1937.

16. Anzén, G.: Tuberculin Reactions in Children by Application of Plaster Test, Svenska läk.-tidning. **34**:733 (May 21) 1937.

17. Hart, F. D.: Tuberculin Patch Tests in Children, Lancet **2**:609 (Sept. 10) 1938.

18. Steward, W. D.: The New Tuberculin Patch Test, J. Pediat. **13**:510 (Oct.) 1938.

19. Brown, M. H.: The Tuberculin Patch Test, Canad. Pub. Health J. **30**:36 (Jan.) 1939.

20. Court, D.: A Comparative Study of the Tuberculin Patch Test and the Intracutaneous Mantoux Test in Childhood, Brit. M. J. **1**:824 (April 22) 1939.

discrepancy between the results of the intradermal and those of the patch test and stated that in at least 95 per cent of cases infection with tuberculosis could be exposed by the latter method. Anthony [21] admitted the reliability of the patch method but called attention to the pruritus and severe local reactions which may follow its use. Wiener and Neustadt [22] obtained 95 per cent as many positive reactions with the patch test as with a Mantoux test done with a 1:1,000 dilution of old tuberculin. Pearse, Fried and Glover [23] found a high degree of correlation between the results of the two tests. Hughes [24] recommended the tuberculin patch test in preference to the intradermal test performed with the first strength purified protein derivative. This view is at variance with that of Ouyang,[25] who obtained a greater number of positive reactions with Mantoux tests performed with the two strengths of purified protein derivative than with the patch test.

MATERIAL AND METHODS

Most recent publications on this subject deal exclusively with results obtained with commercial products. There is a need for further studies and evaluation of the patch test. With this aim in view, this test was performed routinely with a noncommercial preparation on 1,000 consecutive patients admitted to the pediatric service of Queens General Hospital. For comparison, a Mantoux test was done simultaneously in all cases.

The procedure was as follows:

1. A piece of paper towel was placed on a dish or some other smooth surface, moistened with tuberculin and allowed to dry.

2. The paper thus treated with tuberculin was cut into 1 cm. squares. It is advisable to use a forceps in handling the tuberculinized paper instead of the fingers.

3. A strip of adhesive plaster about 2 cm. wide was spread out on a table, and the paper squares were placed on the adhesive surface at intervals, so that they were about 5 cm. apart.

4. The adhesive plaster was then cut into strips, each of which contained a square of tuberculinized paper in the center.

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21. Anthony, P.: The Tuberculin Patch Test, Brit. M. J. **1**:1006 (May 13) 1939.

22. Wiener, S. B., and Neustadt, A.: The Tuberculin Patch Test: A Comparison with the Pirquet and the Mantoux Test, J. Pediat. **14**:752 (June) 1939.

23. Pearse, A. J.; Fried, R. I., and Glover, V.: The Tuberculin Patch Test and the Mantoux Intradermal Test: A Comparative Study of Seven Hundred School Children, J. A. M. A. **114**:227 (Jan. 20) 1940.

24. Hughes, J. G.: The New Tuberculin Patch Test, Memphis M. J. **15**:6 (Jan.) 1940.

25. Ouyang, G.: The Use of Purified Protein Derivative in Tuberculin Patch Test, Chinese M. J. **57**:51 (Jan.) 1940.

5. These strips were laid out on a smooth surface (such as a dish) with the adhesive surface downward. They were stored for use when needed.

6. For the test one of these strips was placed on the back, chest or forearm and allowed to remain for forty-eight hours.

7. The strip was then removed, and the results were interpreted one to two days later.

If the reaction to the test was positive there was an area of reaction characterized by redness, papules and sometimes vesicles, limited to the surface in contact with the tuberculin (fig. 2).

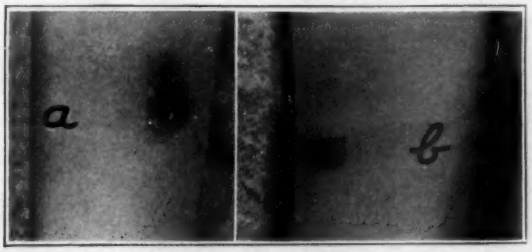

Fig. 2.—Positive reactions to tuberculin tests, showing *a*, result of Mantoux test with 0.1 mg. of a 1:1,000 dilution of old tuberculin, and *b*, result of patch test.

RESULTS

The results are given in the table.

Results of Mantoux and Tuberculin Patch Tests Performed on One Thousand Patients

Diagnosis	No. of Patients	Reactions to Tests: Positive to Mantoux and Patch	Positive to Mantoux and Negative to Patch	Negative to Mantoux and Positive to Patch	Negative to Mantoux and Patch
Unspecified general pediatric service	579	29	3	2	545
Scarlet fever	275	7	0	0	268
Measles	41	1	0	0	40
Pertussis	32	1	0	0	31
Chickenpox	22	0	0	0	22
Diphtheria	17	0	0	0	17
Mumps	13	0	0	0	13
Tuberculosis	11	11	0	0	0
Poliomyelitis	5	0	0	0	5
German measles	2	0	0	0	2
Erysipelas	2	0	0	0	2
Typhoid fever	1	0	0	0	1
Total	1,000	49	3	2	946

Summary

No. of Patients	Reactions to Tests: Mantoux (Intradermal)	Patch
49	Positive	Positive
3	Positive	Negative
2	Negative	Positive
946	Negative	Negative
1,000		

COMMENT

It is thus seen that there was little disagreement between the results of the Mantoux and of the tuberculin patch test. Only in 3 cases was the reaction positive to the intradermal and negative to the patch test. In 2 cases the reaction was negative to the Mantoux test and positive to the patch test. Seven patients with scarlet fever had a positive reaction to tuberculin. None of those with measles had positive reactions. However, in a study reported on by one of us [26] (H. A. R.) in a previous communication some positive reactions to intradermal tuberculin tests were obtained in patients with this disease.

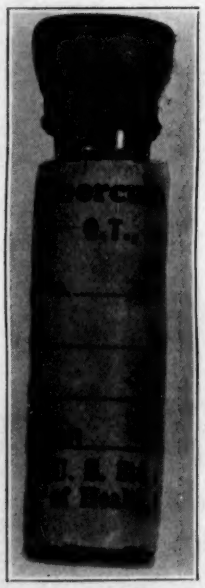

Fig. 3.—Sample vial of the tuberculin supplied to physicians by the Bureau of Laboratories of the New York Department of Health, which can be used for tuberculin patch tests.

The testing material used was Koch's old tuberculin, supplied in vials by the Bureau of Laboratories of the New York Department of Health. Studies by one of us [26] (H. A. R.) have shown that this tuberculin compares more than favorably as to potency and reliability with the product of one of the best commercial houses.

It is to be noted that, although in this series small pieces of paper towel were employed to absorb the tuberculin, any other absorbent

26. Reisman, H. A.: Tuberculin Tests in Children: Comparative Studies with Different Makes of Tuberculin, New York State J. Med. **33**:734 (June 15) 1933.

material can be used for this purpose, such as gauze (Braginskaya [27]), cotton (Lautier,[2] Kasahara [28]), blotting paper (Tuft [29]), filter paper (Bray,[30] Vollmer and Goldberger,[31] Hiro [32]), ointment (Moro,[1] Habetin,[5] Wolf [33]) or fuller's earth and hydrous wool fat (Wright, Chaisson and Allison [34]). No one substance seems to be superior to another. Hart,[17] in comparing the use of the commercial product, which has filter paper as the absorbent of the tuberculin, with the Copenhagen test, in which salve is employed as the carrier of this substance, found that there was little choice between the two with regard to reliability. However, he favored the Copenhagen test because it permitted the amount of tuberculin used to be regulated.

There were no unfavorable reactions from the tuberculin patch test in our series, although there was mild itching in some cases. The usual changes were the production of hyperemia followed by the formation of papules and tiny vesicles, limited to the area of the skin in contact with the tuberculin. After the removal of the adhesive tape any reaction due to it disappears twelve to twenty-four hours later, while that due to the tuberculin becomes more distinct. It is therefore advisable to interpret the results one to two days after removing the adhesive tape. The positive reaction remained visible and usually palpable for about one week, after which it began to fade and became discolored. In some cases a positive reaction could still be recognized several weeks later. In 1 case the reaction to both the tuberculin patch test and the Mantoux test, with 0.1 mg. of a 1 : 1,000 dilution of old tuberculin, was negative, but the reaction became positive when the intradermal test was repeated with 1 mg. of a 1 : 100 dilution. Hence, if the reaction to the tuberculin patch test is negative and there is still a suspicion of tuberculosis, the next procedure should be a Mantoux test done with a 1 : 100 dilution of old tuberculin.

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27. Braginskaya, T. V.: Nathan's Reaction in Tuberculosis, Vrach. delo **20**: 265, 1938.

28. Kasahara, Z.: Ztschr. f. Kinderh. (Referate) **2**:747, 1912.

29. Tuft, L.: Clinical Allergy, Philadelphia, W. B. Saunders Company, 1937, p. 461.

30. Bray, N. W.: Recent Advances in Allergy, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1934, p. 6.

31. Vollmer, H., and Goldberger, E. W.: A New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019 (Nov.) 1937.

32. Hiro, Y.: Ueber meine Tuberkulinpapierprobe, Monatschr. f. Kinderh. **73**: 76, 1938.

33. Wolf, E.: Tuberculin Ointment Patch Test, Am. J. Dis. Child. **47**:764 (April) 1934.

34. Wright, H. P.; Chaisson, A. F., and Allison, R.: Percutaneous Tuberculin Reaction, Am. J. Dis. Child. **56**:1168 (Nov.) 1938.

SUMMARY AND CONCLUSION

The Mantoux and the tuberculin patch test were performed simultaneously on 1,000 patients. Forty-nine had a positive reaction to both the Mantoux and the patch test. Three had a positive reaction to the the Mantoux test and a negative reaction to the patch test. Two had a negative reaction to the Mantoux test and a positive reaction to the patch test.

The noncommercial tuberculin patch test is reliable and compares favorably with the intradermal (Mantoux) test performed with 0.1 mg. of a 1 : 1,000 dilution of old tuberculin.

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STIMULATION OF PERTUSSIS-PROTECTIVE ANTIBODIES BY VACCINATION

A COMPARATIVE STUDY OF PROTECTIVE, AGGLUTINATING AND COMPLEMENT-FIXING ANTIBODIES

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The problem of determining whether pertussis vaccination is effective in preventing whooping cough has been studied for many years. Extensive laboratory investigations have been carried out, but so far no satisfactory method has been developed that can be relied on to determine immunity to this disease. A number of investigators have studied the development of agglutinins and complement-fixing antibodies after vaccination,[1] and some of them considered vaccination successful when a high titer of these antibodies was obtained. Although an increase of these antibodies can usually be obtained when large doses of a potent vaccine are given, there is no evidence that their presence even in high titers is an index of resistance to the disease.

Recent studies have shown that another antibody is stimulated by pertussis infection which may have a direct relation to immunity.

From the Bureau of Laboratories, Department of Health, New York City, and New York Post-Graduate Medical School and Hospital.

1. (*a*) Huenekens, E. J.: The Prophylactic Use of Pertussis Vaccine Controlled by the Complement Fixation Test, Am. J. Dis. Child. **14**:283 (Oct.) 1917. (*b*) Kristensen, M., and Larsen, H. S.: Compt. rend. Soc. de biol. **95**:1110, 1926. (*c*) Kairies, A., and Goetze, S.: Ztschr. f. Kinderh. **55**:551, 1933. (*d*) Bayer, W.: Klin. Wchnschr. **14**:301, 1935. (*e*) Mishulow, L.; Mowry, I., and Orange, R.: J. Pediat. **9**:492, 1936. (*f*) Daughtry-Denmark, L.: Studies in Whooping Cough: Diagnosis and Immunization, Am. J. Dis. Child. **52**:587 (Sept.) 1936. (*g*) Wu, J. P., and Chu, F. T.: Proc. Soc. Exper. Biol. & Med. **38**:693, 1938. (*h*) Miller, J. J., and Silverberg, R. J.: J. Immunol. **37**:207, 1939. (*i*) Lapin, J. H.; Cohen, P., and Weichsel, M.: Arch. Pediat. **56**:590, 1939.

Powell and Jamieson [2] were the first to demonstrate that protective antibodies are present in the serums of patients with pertussis. They tested the serums of 7 patients and found that some of them protected mice against a virulent culture of Haemophilus pertussis. But they considered the mouse protection test "cumbersome" and therefore "of academic interest only." We have described [3] a mouse protection method by means of which pertussis-protective antibodies could be easily detected. We reported that protective antibodies were present in the serums of a large percentage of patients with pertussis after they had whooped three weeks or longer but seldom earlier in the disease and that they were also found after recovery from the disease. Agglutinins were present in the serums of less than one half of the patients who had protective antibodies, and their titers did not correspond either to the duration of the illness or to the titer of protective antibodies. We have been able since then to confirm our earlier observations with regard to the development of protective antibodies after pertussis infection, but we have found that agglutinins and complement-fixing antibodies are seldom present after recovery.[4]

The development of protective antibodies after pertussis infection suggested that these antibodies may also be stimulated by vaccination. If these antibodies could be demonstrated in the serums of vaccinated persons, it would make it possible to determine how soon after vaccination they appear, when they reach the maximum concentration and how long they persist. It would also make it possible to determine the optimum dosage for vaccination, which at present is purely empiric. With this object in view we carried out the following experiments.

EXPERIMENTAL OBSERVATIONS

EXPERIMENT 1

Material and Methods.—A group of 9 children were selected from those attending the Winifred Wheeler Day Nursery. These children were between 2 years 3 months and 5 years 10 months of age, and none of them had a history of pertussis infection or of previous vaccination against pertussis. On reinvestigating their histories later, however, we found that 2 of the children had had four injections of pertussis vaccine one and a half years previously. We decided to include the results for these 2 children in this study in order to see whether their response would differ from that of the children who received a primary vaccination.

A sample of blood was obtained from each of the children before vaccination, and they were then given three subcutaneous injections of our pertussis toxin-vaccine, which contained 10,000,000,000 bacilli per cubic centimeter. The injections were given at seven day intervals, and the three doses consisted of 2 cc., 3 cc.,

2. Powell, H. M., and Jamieson, W. A.: J. Immunol. **32**:153, 1937.

3. Mishulow, L.; Klein, I. F.; Liss, M. M., and Leifer, L.: J. Immunol. **37**: 17, 1939.

4. Mishulow, L., and others: To be published.

and 4 cc., or a total dose of 90,000,000,000 bacilli. One child reacted so severely to the vaccine that the third dose was omitted. This child therefore received only 50,000,000,000 bacilli. Another child contracted mumps soon after the first dose was given, and his vaccination also had to be discontinued. We included the results for both of these children in our study in order to determine whether there was any response to the smaller doses. Beginning approximately three weeks after the last injection of the vaccine, samples of blood were obtained from the children at intervals, and their serums were tested for protective, agglutinating and complement-fixing antibodies.

Preparation of Pertussis Toxin-Vaccine.—Stock cultures of H. pertussis were maintained at 37 C. on Bordet-Gengou medium, and only those were used that were typical both morphologically and culturally. A twenty-four hour growth on Bordet-Gengou medium which contained approximately 33 per cent of sheep blood was emulsified in 1 per cent sheep serum, beef heart broth with a p_H of 6.6 to 6.8, and freshly prepared Bordet-Gengou medium in quart (946 cc.) Blake bottles was inoculated with 4 cc. of the suspension. The bottles were incubated at 37 C. for seventy-two hours. Then sterile physiologic solution of sodium chloride containing 1 per cent phenol was added to the bottles, and the contents of each bottle were examined for purity by smear. The growth was collected aseptically and was again tested for purity by adding some of the bacterial suspension to tubes of Bordet-Gengou medium and beef heart agar and to dextrose broth in fermentation tubes. Care was taken that the phenol contained in the inoculum was sufficiently diluted by the broth so that there would be no inhibition of growth. The vaccine was incubated at 37 C. for twenty-four hours and was then tested for sterility on the mediums mentioned. The material for purity and sterility tests were incubated for seven days.

Each lot of vaccine was tested for toxicity by a method utilizing the Shwartzman phenomenon, as follows: A portion of the vaccine was centrifuged at high speed, and the clear supernatant fluid was passed through a W Berkefeld filter. The filtrate was tested for sterility. Rabbits were given an intracutaneous injection of 0.25 cc. of the filtrate, and eighteen to nineteen hours later they were given an intravenous injection of 1.5 cc. of the same filtrate per kilogram of weight. When the reaction was positive an intense reaction appeared at the point of intracutaneous injection within four to five hours after the intravenous injection. This consisted of induration and an area of intense inflammation, which was reddish black.

The vaccine was diluted with physiologic solution of sodium chloride so that it contained 10,000,000,000 bacilli per cubic centimeter, and it was stored at 8 to 10 C. Care was taken to dilute the vaccine so that the phenol content of the finished product did not exceed 0.5 per cent.

Test for Protective Antibodies.—The method employed was essentially the same as that described in a previous publication.[3] A group of mice weighing 15 to 19 Gm. was used to test each serum. The number of mice in each group was determined by the amount of serum obtained. Whenever possible 8 to 10 mice were used for each serum. The mice were given an injection of 0.2 cc. of the serum into the muscle of a hindleg, and nineteen to twenty hours later they were given an intra-abdominal injection of a virulent culture of H. pertussis suspended in 1 cc. of 4 per cent mucin. The same virulent culture and the same dosage were used in these tests as in our previous investigation. The culture was preserved by drying in the frozen state and remained remarkably constant in virulence. Table 1 shows the virulence of this culture as determined by seven different tests over a period of approximately two years.

Agglutination Test.—We employed the same method in testing for agglutinins as in our previous investigation.[3] The only change made was that the agglutinating antigen was prepared from a twenty-four instead of a forty-eight hour growth on Bordet-Gengou medium. We found that the younger culture gave a smoother and more stable suspension.

Complement Fixation Test.—Antigen: The method of preparing the antigen was the same as that used for agglutination only care was taken to see that all the glassware used was neutral in reaction. The antigen was tested with an anti-pertussis rabbit serum and was so diluted that three times the amount used in the test was not anticomplementary and one fourth of the test dose gave 3 + to 4 + fixation with 3 units of the positive serum.

Complement: Guinea pig serum was used for complement. Not all guinea pig serums could be used in the tests, as some gave nonspecific fixation while others gave weak or no fixation with positive serum. Therefore the serums of several guinea pigs were tested individually for hemolysis and for fixation with the standard dilution of the antigen. Those that were found suitable were pooled and so diluted that 0.1 cc. contained 2 hemolytic units.

TABLE 1.—*Virulence of Strain M42 of H. Pertussis over a Period of Approximately Two Years*

Dose, Millions of Organisms	Number of Mice Which Died in							Period of Illness, Days
	Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Test 7	
500	10/10	10/10	10/10	9/9	10/10	8/10	10/10	2 to 4
250	10/10	10/10	10/10	5/5	10/10	10/10	10/10	3 to 5
125	5/5	5/5	5/5	5/5	7/10	7/10	7/10	4 to 6
62.5	5/5	2/5	5/5	1/5	4/10	4/5	6/10	3 to 7

Test: The subject's serum was inactivated at 56 C. for twenty minutes, and 0.01 cc. and 0.02 cc. quantities were tested for fixation with 0.1 cc. of the standard dilution of the antigen and 0.1 cc. of complement, which contained 2 hemolytic units. Each serum was tested for anticomplementary action in 0.02 cc. and 0.04 cc. quantities without antigen. Controls of the antigen without serum, an antigen titration with a positive serum and an antibody titration of the positive serum were included in each test. The materials for the tests were incubated in a water bath at 37 C. for one hour; then 0.2 cc. of sensitized sheep's red blood cells was added, and the tubes were reincubated for another hour. The hemolytic system was so adjusted that the controls of the antigen without serum were completely hemolyzed in fifteen to twenty minutes. The additional incubation after the controls were hemolyzed helped to rule out doubtful reactions and allowed sedimentation of the unhemolyzed red blood cells in the tubes in which fixation was complete, thus making it easier to read the results. When there was complete fixation in 0.01 cc. and 0.02 cc. of the serum at the end of the incubation period, an antibody titration of the serum was made. The titer of the serum was recorded in terms of the smallest amount of serum that gave complete fixation. The serum was recorded as negative when there was incomplete fixation or none in 0.02 cc., which was the largest amount tested.

Results.—The results of this experiment are summarized in table 2. Table 2 shows that 6 of the 7 children who had had no previous vaccination or pertussis infection had no agglutinins or complement-fixing

antibodies in their serums. The seventh child could not be tested for these antibodies because of insufficient serum. Four of the children also had no protective antibodies and the serums of 2 gave doubtful protec-

TABLE 2.—*Antibody Response to Pertussis Vaccination of Seven Children Who Did Not Have a History of Pertussis Infection or of Previous Vaccination*

Subject	Age	Dose of Vaccine, Millions of Organisms	When Tested	Results				
						Mouse Protection *		
						Actual Survival After Injection of		
				Agglutinin Titer	Complement-Fixing Titer	500 Million Organisms	250 Million Organisms	Total Percentage Survival
C. Z.	4 yr. 5 mo.	90,000	Before vaccination.....	0†	0‡	0/5	0/5	0
			Days after vaccination:					
			22.....	200	0.006	2/5	2/5	40
			43.....	400	0.01	5/5	5/5	100
			109.....	800	0‡	2/4	3/4	62.5
			476.....	400	0‡	1/5	N.T.§	20
B. M.	2 yr. 3 mo.	90,000	Before vaccination.....	N.T.§	N.T.§	0/2	0/2	0
			Days after vaccination:					
			22.....	400	0.005	1/3	1/3	33.3
			109.....	N.T.§	N.T.§	0/2	2/3	40
M. L.	4 yr. 5 mo.	90,000	Before vaccination.....	0†	0‡	0/4	1/4	?
			109 days after vaccination	400	0‡	0/4	3/3	42.8
J. K.	4 yr. 3 mo.	90,000	Before vaccination.....	0†	0‡	0/4	0/5	0
			Days after vaccination:					
			22.....	150	0.007	0/3	3/4	42.8
			43.....	100	N.T.§	2/4	3/4	62.5
			109.....	75	0‡	1/3	3/3	66.6
			476.....	300	0‡	2/5	N.T.§	40
L. S.	4 yr.	90,000	Before vaccination.....	0†	0‡	2/3	1/2	60
			Days after vaccination:					
			22.....	150	0.007	2/5	2/5	40
			43.....	150	N.T.§	2/2	3/3	100
			109.....	600	0‡	0/4	3/4	37.5
J. L.	5 yr. 10 mo.	50,000‖	Before vaccination.....	0†	0‡	1/5	0/5	0
			Days after vaccination:					
			30.....	400	0.005	2/5	5/5	70
			50.....	300	N.T.§	3/3	3/3	100
A. G.	3 yr. 8 mo.	20,000¶	Before vaccination.....	0†	0‡	0/5	0/5	0
			Days after vaccination:					
			35.....	10	0‡	1/5	2/5	30
			56.....	25	N.T.§	2/5	3/5	50
			122.....	37.5	0‡	0/5	0/4	0
			488.....	N.T.§	0‡	0/4	N.T.§	0

* For the mouse protection test 0.2 cc. of the subject's serum was used.

† In this table and in table 3 the zero signifies that there was no agglutination in a 1:10 dilution.

‡ In this table and in table 3 the zero signifies that there was incomplete fixation or none in 0.02 cc. of serum.

§ In this table and in table 3 N.T. signifies not tested, because of insufficient serum.

‖ This child's reaction to the vaccine was so severe that only two injections were given.

¶ This child contracted mumps; so he received only one injection of vaccine.

tion, as only 1 mouse survived in each group, which happens occasionally when groups of mice are given injections of the culture without serum. The serum of 1 child, however, protected 3 of 5 mice although he presumably had had no previous infection or vaccination.

After vaccination all of the children who had received 50,000,000,000 to 90,000,000,000 bacilli showed protective, agglutinating and complement-fixing antibodies when they were tested twenty-two to thirty days after the last injection of the vaccine. The child who received only one injection of the vaccine, of 20,000,000,000 bacilli, also had some protective antibodies thirty-five days after vaccination, but he had a very low titer of agglutinating antibodies and no complement-fixing antibodies.

We had planned to test these children at regular intervals, but because of unforeseen difficulties we were not able to do so and therefore could not determine accurately when the various antibodies attained their maximum concentration. The children were tested between one and one-half and two months after vaccination. Their protective antibodies apparently had reached a maximum concentration at that time, although the titers in the different subjects varied considerably. The titers of agglutinins were fairly high, but they also varied for the different children. Only 1 child was tested for complement-fixing antibodies, and although they were still present the titer had decreased.

The 5 children who received 90,000,000,000 bacilli were retested three and one-half months after vaccination. All of them had protective and agglutinating antibodies but no complement-fixing antibodies. Two of these children were tested again fifteen and one-half months after vaccination, and both of them still had protective and agglutinating antibodies, but the titer of protective antibodies had greatly diminished.

We were not able to retest the child who received 50,000,000,000 bacilli after two months, when he had attained a high titer of protective and agglutinating antibodies, and therefore we could not determine how long his antibodies persisted.

The child who had only one injection, of 20,000,000,000 bacilli, attained a titer of 50 per cent protection within two months, but he had no antibodies when he was tested after four and one-half months. This child's serum was low in agglutinins and had no complement-fixing antibodies during the entire period of testing.

EXPERIMENT 2

Several of the children that we vaccinated were revaccinated fifteen and one-half months after the primary vaccination, but blood was obtained from only 2 of them. One of these 2 children was tested approximately three and one-half and four and one-half months after revaccination and the other after seven months. The results obtained for these children are given in table 3, together with those for the 2 children who gave a history of previous vaccination.

The first 2 children for whom data are listed in table 3 had had four injections of our pertussis toxin vaccine approximately one and one-half years previously. The total dose given at that time was

13,500,000,000 bacilli. Both of these children had a high titer of protective antibodies at the time of revaccination but no complement-fixing antibodies; 1 of them had a low titer of agglutinins, and the other had none. These 2 children were given three weekly injections of our pertussis vaccine, or a total dose of 90,000,000,000 bacilli. When they were tested twenty-three days after the last injection of the vaccine their serums protected all of the mice tested, and they had high titers of agglutinating and complement-fixing antibodies. Three and one-half months after vaccination their agglutinins had increased, and although

TABLE 3.—*Antibody Response of Four Children to Pertussis Revaccination Performed Fifteen to Eighteen Months After Prophylactic Vaccination*

				Results				
						Mouse Protection *		
						Actual Survival After Injection of		
Subject	Age	Dose Used for Revaccination, Millions of Organisms	When Tested	Agglutinin Titer	Complement-Fixing Titer	500 Million Organisms	250 Million Organisms	Total Percentage Survival
B. M.	3 yr. 10 mo.	90,000	Before revaccination.....	75	0	2/5	5/5	70
			Days after revaccination:					
			23.....	4,000+	0.002	3/3	4/4	100
			109.....	4,800	0.01	2/4	4/4	75
L. B.	4 yr. 7 mo.	90,000	Before revaccination.....	0	0	4/5	5/5	90
			Days after revaccination:					
			23.....	300	0.002	2/2	2/2	100
			43.....	300	0.006	5/5	4/5	90
			109.....	900	0.01	3/5	4/5	70
J. K.	5 yr. 7 mo.	20,000	Before revaccination.....	300	0	2/5	N.T.	40
			Days after revaccination:					
			98.....	75	0	3/4	4/5	77.7
			145.....	400	0.02	4/5	6/6	90.9
A. G.	5 yr.	20,000	Before revaccination.....	N.T.	0	0/4	N.T.	0
			217 days after revaccination	800	0.02	3/4	4/4	87.5

* For the mouse protection test 0.2 cc. of the subject's serum was used.

the protective and complement-fixing antibodies had decreased they were still at a high level.

The third child in this group (J. K.) had received 90,000,000,000 bacilli of our vaccine on primary vaccination fifteen and one-half months previously (table 2). He still had protective and agglutinating antibodies, but no complement-fixing antibodies at the time of revaccination. He was revaccinated with 20,000,000,000 bacilli in one injection and was tested approximately three and one-half months later. His titer of protective antibodies had increased, but he had a low titer of agglutinating antibodies and no complement-fixing antibodies. When he was retested four and one-half months after revaccination, his protective and agglutinating antibodies had increased and he also had complement-fixing antibodies.

The fourth child (A. G.) for whom data are listed in table 3 had had only a small dose of our vaccine fifteen and one-half months previously (table 2). He had no protective or complement-fixing antibodies at the time of revaccination, and he was not tested for agglutinins because of insufficient serum. He was revaccinated with 20,000,000,000 bacilli in one injection. When he was tested seven months after revaccination he had a high titer of protective and agglutinating antibodies and had complement-fixing antibodies as well.

EXPERIMENT 3

We planned to study in this experiment the response to pertussis vaccination of infants and young children. Samples of blood were obtained before vaccination from 22 children at the dispensary of the Misericordia Hospital, through the cooperation of Dr. Thomas E. Waldie and Dr. Arthur Buscini. Thirteen of these children were between 7 months and 1½ years of age and 9 were between 2 and 6 years. None of them had a history of pertussis infection or of previous vaccination against pertussis. The samples of blood obtained before vaccination were tested for protective antibodies, and all of them were found to be negative. Because there was insufficient serum we were not able to test them all for agglutinins and complement-fixing antibodies, but tests of the serums of 11 children for agglutinins and of 6 for complement-fixing antibodies all gave negative results.

These children were given three weekly injections of our pertussis vaccine. The doses were 2 cc., 3 cc. and 3 cc., or a total of 80,000,000,000 bacilli. But after vaccination most of the parents refused to allow us to take additional samples of blood from the children. We were able to obtain one sample from each of 4 vaccinated children soon after vaccination. Three of these 4 children were tested two to four weeks after vaccination, and all of them had protective antibodies; 2 of them also had agglutinins, and 1 had complement-fixing antibodies two weeks after vaccination. The fourth child was tested eleven days after vaccination. He had a high titer of agglutinins but no protective or complement-fixing antibodies.

Although we could not carry through this experiment according to plan, it gave us an opportunity to test another group of young children, including infants, who did not have a history of pertussis. The results obtained in this experiment showed that infants and children under 2 years of age who had not had the infection had no pertussis antibodies, and it confirmed the results obtained in the first experiment, in which it was shown that young children who have not had pertussis seldom have pertussis antibodies. The response to vaccination of the 4 children in this group was also in accord with our results in the first experiment in that protective antibodies were present within one month after

vaccination. It seems that two weeks is the minimum period which must elapse after vaccination before protective antibodies will be found in the circulation.

COMMENT

The results obtained in this investigation show that children who have had no pertussis infection or vaccination seldom have pertussis antibodies. Of 29 infants and children between 7 months and 6 years of age who did not have a history of pertussis, only 1 child, who was 4 years old, had protective antibodies, and none of the children tested had agglutinins or complement-fixing antibodies. Ten of the children who had no pertussis antibodies and the 1 child who had protective antibodies only were vaccinated with our pertussis toxin vaccine. After vaccination all of the children who were tested two to five weeks after the last injection of the vaccine had protective and agglutinating antibodies, and 7 of 9 children tested also had complement-fixing antibodies. One of the 2 children who had no complement-fixing antibodies received only 20,000,000,000 bacilli, and he showed a poor response in protective as well as in agglutinating antibodies. The child who had protective antibodies, but no agglutinins or complement-fixing antibodies before vaccination had a high titer of agglutinins and complement-fixing antibodies after vaccination, and his protective antibodies had greatly increased. One of the children was tested eleven days after vaccination. He had a high titer of agglutinins but no protective or complement-fixing antibodies.

The maximum concentration of protective antibodies was attained between one and two months after vaccination, although the height of the titer varied considerably with the individual children. The maximum concentration of complement-fixing antibodies was attained within one month after vaccination. There was considerable fluctuation in the agglutinin titers of the individual children, but in most of the subjects the titer was high soon after vaccination.

The antibody response to vaccination and the length of time that the antibodies persisted were largely proportional to the dose of the vaccine given. The child who received one injection of 20,000,000,000 bacilli had some protective antibodies within two months after vaccination, but he had none in four and a half months. He had no complement-fixing antibodies, and his agglutinin titer was low throughout the period of testing.

The child who received 50,000,000,000 bacilli in two injections responded with a high titer of protective, agglutinating and complement-fixing antibodies thirty days after vaccination, and his protective antibodies attained a maximum concentration within two months. We were not able to obtain any further samples of blood from this child and therefore could not determine how long his antibodies persisted after vaccination.

The children who were vaccinated with 90,000,000,000 bacilli responded with a rapid development of antibodies. Twenty-two days after the last injection of the vaccine, protective, agglutinating and complement-fixing antibodies were present in fairly high titer. Their protective antibodies were at a maximum within two months, and they were still at a high level three and a half months after vaccination, except in 1 child, in whom they had decreased. Two of the children in this group still had protective and agglutinating antibodies fifteen and a half months after vaccination, but their titers of protective antibodies were greatly decreased. Their complement-fixing antibodies were at a maximum within one month after vaccination, but they had disappeared after three and a half months. These results are in agreement with those obtained by Lapin, Cohen and Weichsel,[11] who found that a large percentage of their vaccinated children had complement-fixing antibodies four weeks after vaccination but none had them after four months. Daughtry-Denmark[1f] found that practically 100 per cent of their vaccinated children had complement-fixing antibodies one week after the last injection of a large dose of vaccine but that the number had decreased considerably five months after vaccination.

We tested 4 more children who had been vaccinated one and a half to four years previously. Two of these children had been vaccinated with the Sauer vaccine (90,000,000,000 organisms), 1 three years and the other four years before. Both of them had a low titer of protective antibodies and a high titer of agglutinins but no complement-fixing antibodies. The other 2 children had been vaccinated one and a half years previously with our pertussis toxin vaccine (13,500,000,000 bacilli) during an outbreak of pertussis in the day nursery where they were kept. These 2 children had a high titer of protective antibodies, but they had no complement-fixing antibodies, and only 1 of them had agglutinins. Thus the 6 children who were tested fifteen and a half months to four years after vaccination all had protective antibodies, and 5 of the 6 also had agglutinins. None of them had any complement-fixing antibodies.

Although the indications are that protective and, in most instances, agglutinating antibodies persist for a long time after primary vaccination, no definite conclusions can be drawn at this time, since 4 of the 6 children who had protective antibodies had not been tested before or soon after vaccination. Protective antibodies may have been present in these children before vaccination as a result of a mild attack of pertussis which may not have been diagnosed. Also it is difficult to rule out subsequent exposure to pertussis in a crowded city over a long period, which might have restimulated these antibodies. To determine this point it would be necessary to vaccinate a group of children who have no pertussis antibodies, test them within two months after vaccination and follow them closely for the period of the test. Children in an institu-

tion would be especially suitable for such a test, since they would not be subject to unknown exposure to pertussis. It also remains to determine what concentration of protective antibodies is required to give complete protection.

The stimulation of pertussis antibodies by revaccination also seemed proportional to the dose of the vaccine. When a total of 90,000,000,000 bacilli was given in three weekly injections, there was immediate stimulation of protective, agglutinating and complement-fixing antibodies, and all three antibodies remained at a high level for the period of the test (three and a half months). One injection of 20,000,000,000 bacilli also stimulated all of these antibodies, but they appeared very slowly. The length of time that the antibodies persisted after revaccination and whether they remained longer when the larger dose of vaccine was used have not as yet been determined.

The titers of agglutinating and complement-fixing antibodies of the vaccinated children did not parallel their titers of protective antibodies in the height which they attained, in the time at which they reached a maximum or, in the case of the complement-fixing antibodies, in the length of time that they persisted. These results are in accord with those that we obtained in our studies of the development of protective, agglutinating and complement-fixing antibodies during and after pertussis infection [5] and in our investigations of the protective and agglutinating antibodies in antimeningococcus therapeutic serums.[6] It is difficult to determine what significance agglutinins and complement-fixing antibodies have in the mechanism of immunity, but from the evidence at hand it seems clear that they cannot be taken as an index of immunity to pertussis, since they are seldom present after recovery from the disease, when immunity is high.

The development of protective antibodies, on the other hand, seems to parallel the development of immunity after infection. Therefore the demonstration of protective antibodies after vaccination promises to provide a reliable method for determining whether vaccination has been successful. It will also make it possible to select for vaccination children who have no resistance, since selection on the basis of absence of history of pertussis is not always reliable. We found 3 children with a high titer of protective antibodies among the 31 children who did not have a history of pertussis infection or of previous vaccination. It was only on reinvestigation that the information was elicited that 2 of these children had been vaccinated one and a half years previously. It is hoped that this method will make it possible to determine the optimum dosage of vaccine for the production of prolonged immunity and the time after vaccination at which the children should be reimmunized.

5. Mishulow, Klein, Liss and Leifer.[3] Mishulow and others.[4]

6. Mishulow, L.; Melman, M., and Sklarsky, R.: J. Lab. & Clin. Med. **21**: 406, 1936.

SUMMARY AND CONCLUSIONS

The production of pertussis-protective antibodies was stimulated rapidly by vaccination. When a dosage of 90,000,000,000 bacilli was used, protective antibodies were present twenty-two days after the last injection of the vaccine. These antibodies attained a maximum concentration between one and two months after vaccination, and they were still present in some of the children fifteen and a half months to four years later.

The formation of agglutinins and complement-fixing antibodies was also stimulated rapidly when the foregoing dosage was used. Complement-fixing antibodies attained a maximum concentration within one month but disappeared within three and a half months after vaccination. Agglutinins reached a fairly high titer in most of the children soon after vaccination and remained at a high level for the period of the test. The titers of agglutinating and complement-fixing antibodies did not parallel the titer of protective antibodies of the vaccinated children.

Evidence is presented that protective antibodies develop consistently after infection and that agglutinating and complement-fixing antibodies do not. Therefore the demonstration of protective antibodies after vaccination promises to provide a reliable method of evaluating the efficacy of vaccination against pertussis, provided further tests will show that children who possess protective antibodies are resistant to the disease.

Protective antibodies are present in considerable strength one month after vaccination and seem to be at a maximum within two months after vaccination. Sauer's [7] suggestion of allowing a period of four months for acquiring immunity to pertussis after vaccination seems not to be well founded, in the light of the results which we obtained in this investigation.

The potency of pertussis vaccines and the optimum dosage for human vaccination can now be determined with a measure of certainty, since the development of protective antibodies after vaccination can be easily followed. If the protective antibodies should not be at a sufficiently high level within two months after vaccination, another series of injections would probably bring them up to maximum concentration.

The mouse protection test may also be of value in the selection of susceptible children for vaccination, since absence of a history of pertussis infection cannot always be relied on.

Present indications are that a total dose of 90,000,000,000 bacilli is adequate for stimulating the development of a significant titer of protective antibodies in children.

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7. Sauer, L.: New England J. Med. **213**:1061, 1935.

Case Reports

COMBINED COD LIVER OIL AND LIQUID PETROLATUM PNEUMONIA IN A CHILD

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The purpose of this study is to present an instance of pneumonia brought about by two different oils and to evaluate the simple histochemical method used for the differentiation of the two substances. Although there are many cases of oil pneumonia on record, there are only a few in which the identity of the particular oil involved was determined.

There are available several histochemical fat stains, among which are sudan IV, nile blue sulfate, osmic acid and the Ziehl-Neelsen stain. The use of these stains, singly or in combination, on both frozen and paraffin sections provides an unusually valuable tinctorial method of distinguishing between several oily substances. It must be remembered, however, that these methods cannot supplant the physicochemical analysis of oils extracted from the involved lungs. The latter method was first used by Fischer-Wasels,[1] in 1933, and was extensively applied by Graef [2] in 1939. Chemical methods of analysis are costly and time consuming, and most laboratories of pathology are technically unequipped for carrying out such procedures. It is therefore essential that there be available a simpler, yet accurate, alternative method of differentiating oil pneumonias histologically.

A review of 56 articles published since 1925 reveals that a total of 411 cases of oil pneumonia have been reported. Of these, necropsy was performed in 252. The frequency of each oily substance as the cause of the pneumonia has been indicated in table 1. In only approximately 20 per cent of the cases was an attempt made to identify the oil involved by chemical or histochemical methods. Consequently this table has been based primarily on the clinical implications and the discovery of intrapulmonary oil at necropsy. Table 1 shows that in 98 per cent of the cases the pneumonia was due to liquid petrolatum, cod liver oil, butter fat from milk and its derivatives and iodized poppyseed oil.

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1. Fischer-Wasels, B.: Tödliche Lungenschrumpfung durch Gebrauch von Mentholöl, Frankfurt. Ztschr. f. Path. **44**:412, 1933.

2. Graef, I.: Studies in Lipid Pneumonia, Arch. Path. **28**:613 (Nov.) 1939.

In table 2 certain chemical constants of these four oily substances and their histochemical tinctorial reactions to the staining methods previously mentioned are correlated. Brief examination reveals the simplicity of the differentiation. Liquid petrolatum and iodized poppyseed oil are distinguished by their yellow-pink-orange reaction to sudan IV, their inability to stain with osmic acid and the Ziehl-Neelsen stain and their

TABLE 1.—*Frequency of Occurrence of Various Oils as the Cause of Pneumonia in Two Hundred and Fifty-Two Cases in Which Necropsy Was Performed*

Oil	Frequency		
	Number	Percentage	
Liquid petrolatum	171	68	98%
Cod liver oil *	59	23.4	
Butter fat (from milk and derivatives)	12	4.8	
Iodized poppyseed oil	5	1.8	
Castor oil	2	0.8	
Viosterol in oil	1	0.4	
Olive oil	1	0.4	
Cottonseed oil	1	0.4	

* Includes 1 case in which halibut liver oil was incriminated.

TABLE 2.—*Chemical Constants and Tinctorial Reactions of Four Oily Substances*

	Liquid Petrolatum	Iodized Poppyseed Oil	Cod Liver Oil *	Butter Fat
Iodine number	0	0	137-166	26-28
Acid value	0	0	1.6-5.6	0.45-35.4
Reaction to:				
Sudan IV	Yellow-pink-orange	Orange-red	Orange-red	Orange-red
Nile blue sulfate	Pink	Pink	Blue	Blue
Osmic acid	0	0	Black	Black
Ziehl-Neelsen stain	0	0	Red-purple	0

* The properties of halibut liver oil are identical.

pink reaction to nile blue sulfate. Butter fat stains blue with nile blue sulfate and black with osmic acid, which distinguishes it from the previous two substances. Cod liver oil is identified by its red-purple reaction to staining by the Ziehl-Neelsen method in both frozen and paraffin sections. However, when an oily substance in the lungs stains like butter fat the differentiation ceases, because maize, castor, olive, cottonseed and other oils stain in an identical manner.

Table 3 indicates the frequency of occurrence of various combinations of oils as the cause of pneumonia in cases reported in the literature

in which the diagnosis of oil pneumonia was made either clinically or at necropsy. One can readily see that in each case at least two oils could have been identified as being simultaneously present. However, it is easy to conceive of combinations of oily substances in which differentiation of the constituents would be impossible by these methods. It is suggested that when such conditions prevail and differentiation becomes necessary reliance must be placed on the extraction and chemical analysis of the oily substances from the involved lungs.

TABLE 3.—*Frequency of Occurrence of Combinations of Oils as the Cause of Pneumonia in Reported Cases*

Combination of Oils	Number of Occurrences
Cod liver oil and liquid petrolatum	29
Butter fat and cod liver oil	4
Cod liver oil, liquid petrolatum and butter fat	1
Liquid petrolatum and viosterol * in oil	1
Cod liver oil, liquid petrolatum and viosterol * in oil	1
Castor oil and liquid petrolatum	1
Olive oil and liquid petrolatum	1
Cottonseed oil and liquid petrolatum	1

* The viosterol was contained in a maize or corn oil base.

TABLE 4.—*Age of Patient in Reported Cases of Oil Pneumonia*

Age, years	0-2	2-9	10-19	20-29	30-39	40-49	50-59	60 and Over
Number of patients with pneumonia due to:								
Liquid petrolatum	44	7	1	2	7	12	17	47
Cod liver oil	32	3	0	0	0	1	0	1
Butter fat	7	0	0	0	0	0	0	0

Table 4 gives the age distribution of the patients in the reported cases of oil pneumonia in which the age was stated. The preponderance of very young and distinctly older patients reflects the frequent occurrence of regurgitation and aspiration in the former and of the dysphagia of chronic debilitating diseases in the latter. It again illustrates that care must be taken in the administration of oily preparations to patients in these particularly vulnerable age groups.

REPORT OF A CASE

The following case [2a] is reported to illustrate the importance of the histochemical staining methods for purposes of differentiation.

B. P., a prematurely born Negro boy, weighed 3 pounds 9 ounces (1,562 Gm.) at birth. A roentgenogram of the chest taken at 6 months of age, because of recurrent

2a. Dr. J. R. Gerstley gave permission for the clinical record to be used.

infection of the upper respiratory tract and cough, revealed consolidation of the upper lobe of the right lung. The reaction to a test with tuberculin was negative, and because of the course and the lesions demonstrated by the roentgen examination a diagnosis of "atypical pneumonia" was made at that time.

At 7 months of age he was admitted again, with bronchopneumonia, from which recovery was slow and incomplete. At 10 months of age a roentgenogram showed some residual pneumonic changes in the upper and middle pulmonary fields of the right lung. At 14 months of age he was again admitted, because of repeated attacks of cough and fever and failure to gain weight. At this time a diagnosis of "lipoid pneumonia" was made, principally because of a dietary history which revealed the oral administration of cod liver oil over the previous thirteen and one-half weeks. On numerous occasions he had vomited the oil after it was administered.

At 15 months of age he returned with evidence of another attack of bronchopneumonia, rales and dulness being present over all lobes. He remained in the hospital for two months, during which fever was irregularly remittent, the temperature fluctuating between 101 and 104 F. Repeated sputum cultures revealed pneumococci types III and VIII. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given without success. The respirations became increasingly labored, coarse rales appeared throughout both pulmonary fields and death occurred two months after admission, at 17 months of age. Repeated roentgenograms during the last two months showed increasing bilateral pulmonary consolidation of both the upper and the lower lobe.

Necropsy was performed three hours after death. The body was poorly developed and nourished. There was no free fluid in any of the serous cavities. The right pleura was gray-white and thickened over the apex but otherwise was smooth and glistening. The right lung was extremely firm, especially at the apex, and contained numerous firm yellow areas measuring up to 4 cm. in diameter. These were most numerous posteriorly and in the perihilar regions. The remainder of the right lung about these areas was hemorrhagic. The left pleura was smooth and glistening. The upper and lower lobes of the left lung were filled with similar firm yellow nodules. The hilar lymph nodes measured up to 1 cm. in diameter and on section were yellow-pink and soft. There were cloudy swelling of the myocardium and passive hyperemia of the liver and the spleen.

Microscopic study of the lungs revealed the often described typical structure of an acute and chronic interstitial type of oil pneumonia. The oil was found both free and in large macrophages. In the perihilar regions extensive parenchymatous fibrosis was noted. In addition, acute hemorrhagic bronchopneumonia was present within the intervening alveolar spaces.

Special studies utilizing the tinctorial methods mentioned revealed two types of oily substance. The first was found as intracellular droplets in the older perihilar lesions. The substance in these droplets stained orange-red with sudan IV, blue with nile blue sulfate, black with osmic acid and reddish purple with the Ziehl-Neelsen stain. The second oil was found diffusely in all lobes and made up the bulk of the intrapulmonary oil. It stained yellow-orange with sudan IV, pink with nile blue sulfate and failed to stain with either osmic acid or the Ziehl-Neelsen stain. Much of this oil was found extracellularly, which indicated its very recent administration.

The conclusion was therefore drawn that the pulmonary condition was a combination of chronic cod liver oil pneumonia and recent liquid petrolatum or iodized poppyseed oil pneumonia. From the history it

was known that cod liver oil had been administered for at least fourteen months but that it had not been given more recently than three months before death. During the patient's last hospitalization 1.5 ounces (45 cc.) of liquid petrolatum had been given daily for twenty-seven days, for persistent constipation. A total of 45 ounces (1,331 cc.) of liquid petrolatum had been used up to the day before death. It was not suspected that the latter agent had been responsible for the increasing pulmonary consolidation until the histochemical studies were completed. The child's death, which was caused by severe acute hemorrhagic bronchopneumonia, was in no small measure precipitated by the aspiration of the liquid petrolatum administered during the last stay in the hospital.

This case illustrates the value of this simple histochemical method in the differential diagnosis of combined oil pneumonias. Without it, this case probably would have been recorded as an instance of bronchopneumonia superimposed on cod liver oil aspiration pneumonia, without suspicions being aroused of the more important role played by the aspiration of liquid petrolatum.

COMMENT

Over the past sixteen years, since the first reported case of oil pneumonia in a human subject, numerous names have been applied to this distinctive pulmonary alteration. Most recently, Graef suggested the name "lipid pneumonia," because of its etymologic correctness. This term, however, still seems inadequate in view of the fact that the term "lipid" chemically does not include the hydrocarbon liquid petrolatum, which was the causative agent in 68 per cent of the reported cases of oil pneumonia. For want of a better term, it is suggested that the all-inclusive name "oil pneumonia" be restored.

Sudan IV (scarlet red) has supplanted sudan III (Daddi) in usefulness as a routine oil stain because of the deeper color and sharper contrast it produces and its shorter staining time. Its solubility in liquid petrolatum is 20 per cent of that in vegetable and animal oils. Therefore, when examples of these two types of oil are simultaneously present with liquid petrolatum the contrast in color becomes differentially valuable. The commercial nile blue sulfate in addition to the pure dye contains a red, oil-soluble oxazone derivative. The pure dye is not soluble in oil, but it combines readily with free fatty acids, coloring them blue. The oxazone derivative colors neutral oils pink. The acid values of the oils listed in table 2 explain clearly why liquid petrolatum and iodized poppyseed oil are stained pink, while cod liver oil and butter fat from milk derivatives are stained blue, with nile blue sulfate. Osmic acid becomes valuable as a differential stain because of its reducibility to black metallic osmium

by oleic acid and its derivatives, which are contained in almost all animal and vegetable oils. The oils containing these are in turn blackened or browned by the precipitated osmium. The iodine number indicates the content of unsaturated fatty acids, of which oleic acid is a member. Reference to table 2 makes clear the difference between the reactions of liquid petrolatum and iodized poppyseed oil to staining with osmic acid and those of cod liver oil and butter fat from milk derivatives.

In 1928 Pinkerton,[3] in a series of intrapulmonary experimental studies, first noted that cod liver oil in the lungs undergoes an alteration of its chemical structure. It becomes insoluble in the usual oil solvents and resists decolorization with acid alcohol after staining with basic carbolfuchsin (Ziehl-Neelsen stain). In 1938 Graef, Kaufmann and Kaplan [4] demonstrated by histochemical methods that this acid-fast material was in all probability an insoluble lipoprotein complex. During the past three years Hass [5] has confirmed this observation by extensive experiments.

This transformation, which occurs in the lungs of both human subjects and experimental animals with cod liver oil pneumonia, makes the histochemical method of diagnosis absolutely essential. In the case reported here, all of the cod liver oil present in the lung had already become acid fast and was shown to be insoluble in the usual oil solvents. If only extraction with oil solvents and subsequent physicochemical analysis of the oil obtained had been performed, the presence of cod liver oil would have been completely missed. It is urged, therefore, that simultaneous histochemical studies be carried out even in those instances in which extraction and analysis of the oil are performed.

In conclusion, one may say that if sudan IV alone had been used to identify the intrapulmonary oil in the case reported only the historically implicated cod liver oil would have been incriminated. If only physicochemical analysis had been used to identify the oil only liquid petrolatum would have been isolated. With the use of the histochemical method described it was possible to identify the two oils and to prove that they were present simultaneously.

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3. Pinkerton, H.: The Reaction to Oils and Fat in the Lung, Arch. Path. **5**: 380 (March) 1928.

4. Graef, I.; Kaufmann, W., and Kaplan, L.: Experimental Studies of Tissue Reactions to Lipids, Arch. Path. **26**:914 (Oct.) 1938.

5. Hass, G. M.: Tissue Reaction to Natural Oils and Fractions Thereof, Arch. Path. **26**:956 (Nov.) 1938; Hydrolysis of Esters in the Intercellular Medium, ibid. **26**:1183 (Dec.) 1938; Intercellular Transformations of Unsaturated Fatty Acids and Esters, ibid. **26**:1196 (Dec.) 1938; Membrane Formation at Lipoid-Aqueous Interfaces in Tissues, ibid. **27**:15 (Jan.) 1939; Membrane Formation at Lipoid-Aqueous Interfaces in Tissues, ibid. **28**:177 (Aug.) 1939.

SUMMARY

A case of combined cod liver oil and liquid petrolatum pneumonia in a child of 17 months is reported, and the identification of the oils by a histochemical method utilizing sudan IV, nile blue sulfate, osmic acid and the Ziehl-Neelsen stain is mentioned. The differential value of the histochemical method in the presence of cod liver oil pneumonia is stressed.

COARCTATION OF THE AORTA IN CHILDHOOD

REPORT OF TWO CASES IN WHICH THE DIAGNOSIS WAS CONFIRMED BY THE INTRAVENOUS INJECTION OF DIODRAST

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LOS ANGELES

Coarctation of the aorta is an unusual congenital anomaly which is noted about once in 1,550 autopsies.[1] Bonnet [2] divided the disorder, on the basis of the anatomic lesions, into the so-called infantile and adult types. In the infantile type the coarctation characteristically occurs between the origin of the left subclavian artery and the mouth of the ductus arteriosus. The anomaly may be noted as diffuse narrowing of the isthmus of the aorta, the presence of a mere fibrous cord or the complete absence of the isthmus. The adult type of coarctation is characterized by stenosis of the aorta occurring at or just distal to the insertion of the ductus arteriosus. The ductus is usually obliterated; Abbott [3] found that it was noted as being patent in only 17 of the autopsy reports for the 200 cases she reviewed. In the infantile type the ductus is usually patent, its size being inversely proportional to the lumen of the isthmus, so that in the presence of complete obliteration of the isthmus the ductus may be markedly dilated and continue down to anastomose with the descending aorta. The infantile type is frequently associated with other marked developmental abnormalities of the cardiovascular system and therefore is usually incompatible with life. The adult type is not associated with other severe congenital cardiovascular defects and is characterized by the development of an adequate collateral circulation. An extensive anastomosis develops between branches of the subclavian and the aortic intercostal arteries, as well as between the epigastric and the internal mammary artery. Because of this collateral circulation the adult type is usually compatible with long life, and the case of a patient 92 years of age has been reported.[4]

From the Pediatric Service of Mount Sinai Hospital, New York (Dr. Béla Schick, Director).

1. Blackford, L. M.: Coarctation of Aorta, Arch. Int. Med. **41**:702 (May) 1928.
2. Bonnet, L. M.: Rev. de méd., Paris **23**:108, 1903.
3. Abbott, M. E.: Am. Heart J. **3**:381 and 574, 1928.
4. Reynaud, A.: J. hebd. de méd. **1**:161, 1828.

Bonnet's anatomic classification is desirable, but his terminology is misleading. Bonnet expressed the belief that the infantile type represented a congenital malformation, whereas the adult type developed in extrauterine life, probably as the result of the extension of the obliterative endarteritis of the ductus arteriosus into the wall of the aorta. It is now generally conceded that both types of coarctation are congenital; so the terms infantile and adult are misnomers. In the adult type the lesion is present during infancy and childhood even though it may go unrecognized until later life. The patient survives because of the development of a collateral circulation sufficiently extensive to compensate for the defect in the aorta. We suggest the terms "compensating coarctation" for the variety previously described as the adult type and "noncompensating coarctation" for the infantile type.

Blackford,[1] in his review of the subject, stated that coarctation of the noncompensating type has rarely been diagnosed during life. Such a diagnosis is of only academic interest, since the patient is "doomed to an early death." The diagnosis of the compensating type is of great importance for the future welfare of the patient. This was well demonstrated by Abbott[3] in her report on this subject. In 40 per cent of a series of 196 cases in which the diagnosis was verified at autopsy the patient was between the ages of 16 and 30 years. In about 75 per cent of this group the cause of death was cardiovascular in origin; sudden cardiac failure, cerebral hemorrhage or rupture of the aorta in 40 per cent and gradual progressive heart failure in 35 per cent. Severe exercise was a fairly common precipitating factor in the sudden death of apparently healthy young adults. At autopsy these patients unexpectedly showed rupture of an aneurysm secondary to coarctation of the aorta. In view of these facts accurate diagnosis made as early in life as possible becomes a medical responsibility. It is essential that persons with this congenital abnormality be made aware of their limitations and guided accordingly.

Blackford reported that the anomaly had been recognized clinically in the cases of 4 children up to 1928. Eisenberg[5] in 1938 collected 11 additional cases from the literature and described the cases of 3 additional children, 1 of whom was 2½ years old. We wish to report the cases of 2 patients, 20 months and 12 years of age respectively, and to demonstrate the possibility of visualizing this congenital anomaly with the aid of the intravenous injection of a solution of diodrast.

REPORT OF CASES

CASE 1.—A 20 month old white American-born boy of Puerto Rican parentage was admitted to Mount Sinai Hospital on Dec. 12, 1938 with the complaints of fever, rapid breathing and cough of one week's duration. The family, birth,

5. Eisenberg, G.: J. Pediat. **13**:303, 1938.

feeding and developmental histories were not contributory. Five weeks prior to entry the patient had become ill and had had paroxysms of coughing followed by vomiting, which were probably due to whooping cough. The child was improving until one week before admission, when he became febrile, a nasal discharge developed and his breathing became rapid and labored.

The physical examination revealed an undernourished, acutely ill infant whose breathing was rapid and grunting. The fontanels were closed. There were moderate beading of the costochondral junctions and flaring of the costal margins. The abdomen was distended but not tender, and no masses or viscera were palpable. There was flaring of the alae nasi. Dulness to percussion was noted over the lower half of the right side of the chest anteriorly and posteriorly, and breath sounds in this region were diminished in intensity and high pitched. A few coarse rales were audible. A loud systolic murmur was heard over the entire precordium; it was loudest over the second left interspace but was transmitted to the axilla. A systolic murmur was heard just medial to the angle of the left scapula. The blood pressure in the upper extremities was 110 systolic and 70 diastolic, but no readings could be obtained of the pressure in the lower extremities. No femoral or dorsalis pedis pulsation was observed in the lower extremities, both of which were definitely cooler than the rest of the body.

A diagnosis of pneumonia involving the middle and lower lobes of the right lung and congenital heart disease, probably coarctation of the aorta, was made. Examination of the sputum revealed pneumococcus type 19, and culture revealed Streptococcus haemolyticus. A blood culture was sterile. The reaction to a tuberculin patch test and to a Mantoux test was negative and to a Schick test positive. The hemoglobin content was 65 per cent; the red blood cells numbered 5,150,000 and the white blood cells 27,200, with a marked predominance of polymorphonuclear leukocytes. The urine was normal. The electrocardiogram showed no abnormality. Roentgen examination of the chest showed marked irregular infiltration throughout the right lung, particularly in the lower lobe, where there were small areas of rarefaction. The appearance of the right lung suggested pneumonic infiltration with possible atelectasis of the lower lobe and emphysema of the middle lobe or the lower part of the upper lobe. The appearance of the left lung was within normal limits.

The patient was moderately ill for six days, after which his temperature fell by crisis. The abnormalities in the chest subsequently subsided, and repeated roentgenographic studies showed complete clearing of the pneumonic process.

The following observations referable to the cardiovascular system were made: a loud systolic murmur, heard best over the left second intercostal space; a systolic murmur heard posteriorly in the interscapular area; elevated blood pressure in the upper extremities; failure to obtain readings of the blood pressure in the lower extremities, and inability to feel the femoral or dorsalis pedis pulse, and an easily discernible difference in temperature between the lower extremities and the remainder of the body. On the basis of these observations a diagnosis of coarctation of the aorta was made. There was no roentgenographic evidence of notching of the ribs. Oscillometric readings of 1 to 1½ units were obtained of the blood pressure in the lower extremities.

On March 16, 1939 the patient was seen in the follow-up clinic. The blood pressure in the upper extremities was 170 systolic and 110 diastolic. No readings of the blood pressure in the lower extremities were obtained, and the femoral and dorsalis pedis pulsations were not discernible. A loud systolic murmur was

audible at this time between the scapula and the vertebral column. On subsequent visits a loud systolic murmur was heard posteriorly and a faint systolic murmur anteriorly. The blood pressure in the upper extremities ranged about 150 systolic and 110 diastolic, and no readings of pressure in the lower extremities were obtained.

CASE 2.—E. M., a white boy 12 years of age, was first seen in the outpatient department of Mount Sinai Hospital on March 16, 1940, having been referred to the clinic with a diagnosis of rheumatic heart disease. The family history was noncontributory except that the boy's father was attending the cardiac clinic because he had had coronary thrombosis two years previously. Four siblings were

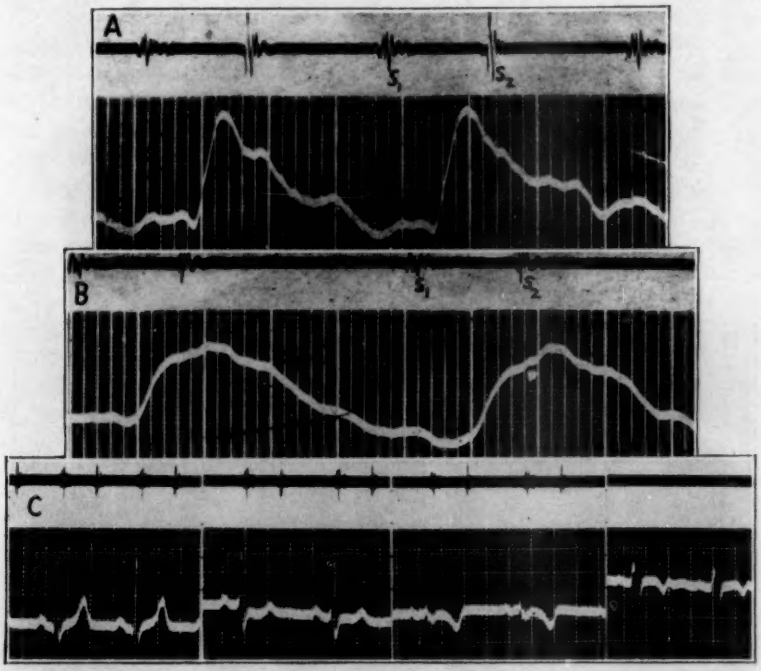

Fig. 1 (case 2).—*A*, tracing of the normal radial pulse; *B*, tracing of the femoral pulse, demonstrating the slow systolic rise and systolic plateau in place of the peak usually seen, and *C*, electrocardiogram, showing left axis deviation and deeply inverted T_3.

living and well. The patient's birth and developmental history were normal. He had received diphtheria toxoid at 2 years and had been vaccinated against smallpox at 8 years of age. He had had scarlet fever, measles, varicella and pertussis. Tonsillectomy had been performed at 6 years of age.

About six or seven months prior to his appearance in the clinic the boy had been examined in school, and his parents had been notified that he had rheumatic heart disease. He was then seen by a private physician, who confirmed the diagnosis and referred the patient to the hospital. His history revealed no evidence of manifestations of rheumatic fever.

Examination showed that he was well developed and well nourished and not acutely ill. His color was excellent. There were several prominent blood vessels over the upper part of the chest and over the lower jaw. Pulsating vessels were noted anteriorly in the second and third interspaces. The heart was not enlarged to palpation or percussion. There was a loud blowing murmur, which was heard best in the second interspace over the sternum and just to the right of the sternum. This murmur was diastolic in time and transmitted upward toward the neck. It could not be heard over the apex. The cardiac rate was 90 per minute and regular. Posteriorly on the right just beneath and mesial to the scapula a loud

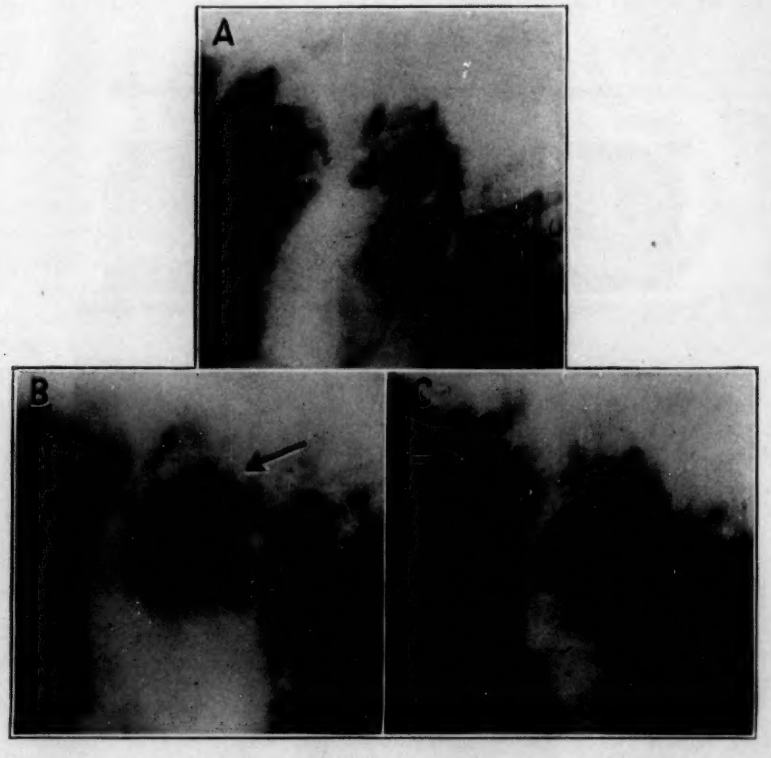

Fig. 2 (case 2).—Roentgenograms of the heart. *A*, taken immediately after the intravenous injection of the contrast medium, demonstrating the filling of the right side of the heart and the pulmonary arteries. *B*, showing filling of the left side of the heart and the aorta. Some of the contrast medium is still visible in the pulmonary vessels; the arrow indicates the site of the coarctation of the aorta. *C*, showing the left side of the heart and the aorta still outlined by the contrast medium. The site of the coarctation is well demonstrated; the pulmonary vessels are now empty. The arrow indicates the dilated internal mammary artery, which usually cannot be visualized.

whistling systolic murmur was heard; deep breathing altered its intensity. Since it was different in timing and character from the precordial murmur, they were thought to originate from different sources. Neither the femoral nor the dorsal

pedis pulsation was discernible. The blood pressure was 165 systolic and 90 diastolic in the left arm, 168 systolic and 95 diastolic in the right arm, 98 systolic and 84 diastolic in the left leg and 96 systolic and 80 diastolic in the right leg. The lungs were normal and the abdomen scaphoid. No masses or viscera were palpable. The genitals were normal, and the testes were descended. The extremities were normal. There were no notable differences in development between the extremities on the right and the left or between the upper and the lower extremities. The throat was normal; the tonsils had been removed. The teeth were in good condition.

Because of the results of the physical examination it was felt that the boy had coarctation of the aorta, and further investigation was advised.

Tracings revealed a normal radial pulse. The femoral pulse wave showed a slow systolic rise and a systolic plateau instead of the peak usually present.

The electrocardiogram (obtained by Dr. A. Master) revealed sinus arrythmia; there was a tendency to left axis deviation; T_3 was deeply inverted, and T_4 was diphasic.

The roentgenogram of the chest was normal.

Roentgen examination of the cardiac chambers after the injection of a contrast medium was carried out by Drs. Sussman, Steinberg and Grishman on April 1. Dr. Sussman reported on the examination as follows: "Opaque visualization of the cardiac chambers demonstrated a narrowing of the aorta at the junction of the arch and the descending portion. The opaque material was seen to be thrust against this narrowed segment, but little passed through. Most of the opaque material passed into the brachiocephalic vessels. There was definite visualization, for example, of the internal mammary artery, which was moderately dilated. The left ventricle was also distinctly dilated."

COMMENT

In arriving at a diagnosis of coarctation of the aorta the following observations are of importance: (1) the presence of murmurs; (2) the presence of enlarged superficial arteries over the upper portion of the body; (3) disproportion between the results of blood pressure determinations and oscillometric examinations for the upper and the lower extremities, as well as failure to obtain the femoral pulse; (4) roentgenographic evidence of changes in the thoracic cage, and (5) actual visualization of the lesion with the aid of an intravenously injected contrast medium. The precordial murmur is of little, if any, assistance. The murmur may be transitory or absent, and when present is of no diagnostic value. In our first case no precordial murmur was noted during several examinations. The presence of a systolic murmur in the interscapular area posteriorly, more frequently on the left than on the right, is, however, of much greater diagnostic significance. Such a murmur may be caused by a stream of blood passing through the dilated and tortuous branch of the brachial artery, which passes beneath the scapula mesially to anastomose with the upper aortic intercostal arteries. The vessel emerges from beneath the muscles of the back and becomes

superficial at the lower angle of the scapula. It is at this site that the murmur is best heard.

The presence of enlarged superficial arteries over the neck and the thorax is important. It is of much greater significance in adults than in children. In case 1 such enlarged vessels were not noted. In case 2 neither infra-red nor ordinary photographs revealed them. They were detected only after close inspection.

Of considerable diagnostic importance is the great disproportion between the blood pressure in the arms and that in the legs. Very often the blood pressure in the lower extremities cannot be obtained and the femoral pulse is not discernible. The simple procedure of attempting to obtain the femoral pulse should therefore be included in every cardiac examination, as was emphasized by Eisenberg.[5] The oscillometric examination deserves mention as a diagnostic aid. Obtaining the pulse and the blood pressure may yield the desired information; however, the oscillometric examination, affording as it does a means of measuring the amplitude of vascular pulsations at levels where feeling the pulse is impossible, offers a more accurate means of obtaining valuable information. Failure to detect pulsation with the oscillometer does not necessarily imply complete absence of circulation, and the detection of minute pulsations does not rule out the diagnosis of coarctation. The difference in the amplitude of the vascular pulsation in the upper extremity as compared with that in the lower extremity is of great significance.

In cases of coarctation of the aorta ordinary roentgenograms of the heart are of no value, since the size and contour of the heart are usually within normal limits. However, one may observe the presence of erosion of the ribs, caused by the enlarged tortuous intercosal arteries, which was noted by Meckel[6] and emphasized by Railsback and Dock.[7] Such erosion evidently takes several years to develop and is therefore seen much more constantly in adults than in children, though it has been noted in children as young as 5 years of age (Lombardi[8]; Eisenberg[5]). In both of our cases roentgenograms of the heart and ribs were entirely normal.

Previously all of the criteria for the diagnosis of coarctation of the aorta have been indirect. It was recognized that if it were possible to visualize during life the site of the coarctation and the shunting of the blood from the aorta through the collateral circulation direct evidence of the presence of the lesion would be available. This has now been accomplished. Many attempts have been made to visualize the cardiac

6. Meckel, A.: Arch. f. Anat. u. Physiol., 1827, p. 345.
7. Railsback, O. C., and Dock, W.: Radiology **12**:58, 1929.
8. Lombardi, Q.: Semana méd. **2**:1004, 1936.

chambers and the great vessels by means of the injection of a contrast medium prior to the taking of roentgenograms. Forssmann [9] in Germany in 1931 introduced a catheter into the vein at the elbow and slowly advanced this in the direction of the heart. He then injected an iodide preparation through the catheter, but his results were poor. Egas Moniz, Lopo de Carvalho and Almeida Lima,[10] the Portuguese investigators, were somewhat more successful in visualizing the pulmonary vessels. They used the same method except that they injected a concentrated solution of sodium iodide. Ameuille [11] and his associates, in 1936, were the first to visualize the right chambers of the heart. Their technic was simply a modification of Forssmann's method in which they used a highly concentrated solution (120 per cent) of sodium iodide. However, they concluded that the method was not suitable for clinical study of the cardiovascular system because of the great technical difficulty encountered. In 1938 Castellanos, Pereiras and Argelio García [12] injected organic iodide compounds into the peripheral veins; their method was the first to obviate the necessity of passing a catheter through the vein to the right auricle. These authors studied children and were able to visualize the pulmonary artery and the right side of the heart. Since the work of Castellanos and his associates improvements in technic have been introduced by Robb and I. Steinberg [13] and by Sussman, M. Steinberg and Grishman.[14] After having had experience with various types of contrast mediums, Robb and I. Steinberg [15] concluded that diodrast was the most desirable. Their procedure consists in rapidly injecting 25 to 45 cc. of a 20 per cent solution of diodrast into a large vein in the arm and taking roentgenograms while the heart and the blood vessels are filled with opaque material. In order to visualize adequately the complete cardiac cycle it is necessary to make several exposures in the very short time the contrast medium remains within the cardiac chambers. This is one of the major technical problems encountered. Sussman, M. Steinberg and Grishman [14] have overcome this drawback in their multiple exposure method, in which they take

9. Forssmann, W.: München. med. Wchnschr. **78**:489, 1931.

10. Egas Moniz, Lopo de Carvalho and Almeida Lima: Presse méd. **39**:996, 1931.

11. Ameuille, P.; Ronneaux, G.; Hinault, V.; Desgrez, and Lemoine, J. M.: Bull. et mém. Soc. méd. d. hôp. de Paris **52**:729, 1936.

12. Castellanos, A.; Pereiras, R., and Argelio García: Seventh Congress of the Panamerican Medical Association, Habana, 1938, pp. 3-74; Bol. Soc. cubana de pediat. **10**:225, 1938.

13. Robb, G. P., and Steinberg, I.: Am. J. Roentgenol. **41**:1, 1939; **42**:14, 1939.

14. Sussman, M. L.; Steinberg, M. F., and Grishman, A.: Am. J. Roentgenol., to be published.

15. Robb, G., and Steinberg, I.: J. Clin. Investigation **17**:507, 1938.

pictures of the image on the fluoroscopic screen with a miniature camera. Using this method they were able to demonstrate the presence of the coarctation of the aorta and the collateral circulation in our case 2.[16]

SUMMARY

Two cases of coarctation of the aorta in which the diagnosis was made during childhood are described. The diagnostic criteria are reviewed, and the possibility of visualizing the lesion by means of the intravenous injection of a contrast medium is demonstrated. The suggestion is made that the terms "compensating" and "noncompensating" coarctation be substituted for "adult" and "infantile" type of coarctation. It is essential that the diagnosis of coarctation of the aorta be made as early in life as possible, so that the patient may be made aware of his physical limitations and guided accordingly. Strenuous exercise should be avoided, and all sports necessitating marked physical exertion must be forbidden.

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2007 Wilshire Boulevard.

16. Grishman, A.; Steinberg, M. F., and Sussman, M. L.: Am. Heart J. **21**: 365, 1941. A discussion of the roentgen aspects of our case 2 is included in this report.

SIRENOMELIAN MONSTER (SYMPUS)

AN ANATOMIC PRESENTATION

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NEW ORLEANS

REPORT OF A CASE

A male sirenomelian (single-limbed) monster was born of white parents at Charity Hospital, New Orleans, on Aug. 23, 1939. The delivery occurred at full term, and the presentation was left sacral anterior. The parents, who had had no other children, knew of no monsters or children with congenital deformity on either side of the family. The infant's heart sounds were normal at birth, but death occurred one hour later.

At necropsy, which was performed three days after death, gross inspection revealed a single-limbed monster with a large umbilical hernia. The body weighed 1,565 Gm. and measured 24 cm. from crown to rump and 39 cm. from crown to toes. There were no discernible abnormalities of the head, neck, thorax or upper extremities. The circumference of the chest was 26 cm. The umbilical hernial sac, which was filled with intestine, measured 5 by 4 by 3.5 cm. in its largest diameters and 2 cm. in diameter at the umbilicus. Above the umbilicus the abdomen measured 23.5 cm. in circumference and showed no abnormality. Below the hernia the abdomen tapered downward until, at the inguinal region, the circumference was 14.7 cm. Slightly below the fold marking the junction of the lower extremity with the trunk were a well formed penis and scrotum; the testes had not descended. A small nodular elevation of the skin, measuring 1 by 0.8 cm. and elevated 0.4 cm. above the skin level (fig. 1), was seen at the level of the last lumbar vertebra, just to the left of the midline. This projection, although freely movable, gave the impression of being attached to the deeper tissues by a cordlike structure.

The distance from the inguinal groove to the knee measured 10.5 cm. and that from the groove to the toes 14 cm. Only the slightest degree of flexion was possible at the hip joint, and rotation was impossible. The lower extremity was curved anteriorly to such a degree that the lower part of the leg was approximately at a right angle to the axis of the trunk. Two well defined bones could be felt in the region of the thigh. The patellar surface of the knee was posterior. Slight ventral flexion was possible at the knee, but isolated movements of either the femurs or the tibial bones at this joint were impossible. Below the knee and extending to the ankle were two large bones (tibias). They could not be rotated at the ankle, but the foot was freely movable at this joint. The texture of the ventral surface of the foot was similar to that of plantar skin. Distally the foot was split into two parts. The left part measured 1.7 cm. in the lateral diameter, 0.9 cm. in the anteroposterior diameter and 1.1 cm. in length. The right part was somewhat smaller, measuring 1.2 cm. in width, 0.8 cm. in thickness and 0.6 cm. in length. Each portion terminated distally in a digit which possessed two freely

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movable phalanges. The terminal phalanges were bent approximately at right angles to the proximal phalanges and were directed to the left.

The diaphragm was intact, and no abnormalities of the stomach were apparent. The liver weighed 60.2 Gm.; it was bilobate, the left lobe being normal in appearance. The right lobe almost filled the right side of the abdominal cavity and extended deep into the pelvis. The gallbladder was normal. The spleen, which weighed 7.7 Gm., was normal in location and appearance, and the pancreas also presented no abnormalities. All of the intestinal coils were on the left side. The small intestine, except for the portion located within the umbilical hernia, was normal in appearance; an appendix vermiformis was not present, and a true ileo-

Fig. 1.—Lateral view of the specimen. The patellas are on the posterior surface. The small nodule containing the lower end of the spinal canal is apparent in the thoracicolumbar region.

cecal junction could not be identified. The total length of the intestine was 114.5 cm., of which 85 cm. was located above the hernia, 10.5 cm. within the sac and 19 cm. below it. The intestine within the hernia was dilated for 4 cm. of its length, the dilatation reaching a diameter of 4.5 cm. at the widest point. The descending colon took a normal course until it terminated suddenly in a blind pouch approximately 2 cm. from where the anal region would normally be. The kidneys were absent, but in their normal position were two adrenal glands, measuring 3.4 by 1.8 by 0.4 cm. and weighing together 7.8 Gm.

The genitourinary organs were rudimentary in appearance (fig. 2). No kidney tissue could be found. The urogenital sinus extended from the umbilicus along

the posterior surface of the anterior abdominal wall to the true pelvis, where its base rested on the anterior surface of the ilium. It was patent throughout, and its lumen was directly continuous with the lumen of the urethra. The penis, which was attached to its anterior surface at the junction of the middle and the lower third, extended downward over the pubic bones and emerged slightly to the left of the midline. In the region of this attachment the urogenital sinus was somewhat thicker than elsewhere, but the lumen showed no dilatation resembling a bladder. At the base of the urogenital sinus, on either side posteriorly, arose the two vasa deferentia, which took a tortuous course laterally and connected with

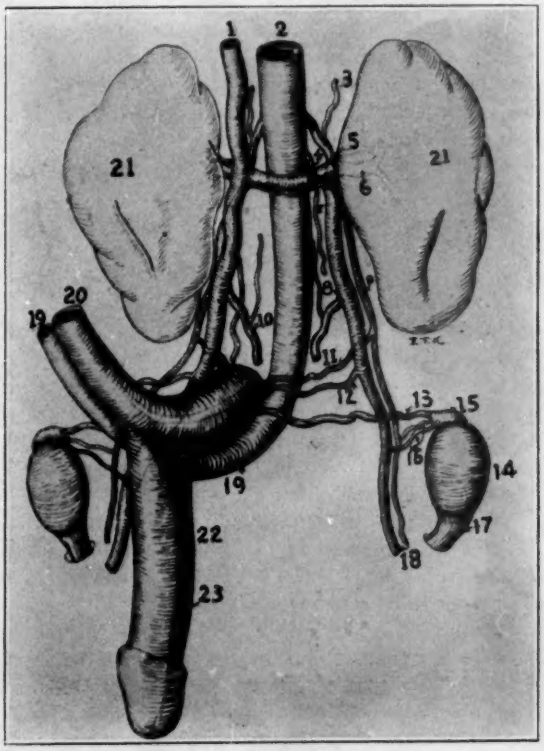

Fig. 2.—Diagram of the genitourinary system and the vascular system of the lower part of the abdomen, showing the postcardinal vein (*1*), the aorta (*2*), the vessels to the muscles of the vertebral column (*3*), the subcardinal anastomosis (*4*), the artery to the adrenal gland (*5*), the vein from the adrenal gland (*6*), the sacral artery (*7*), the subcardinal vein (*8*), the "common iliac" artery (*9*), the vessels from the muscles of the vertebral column (*10*), the artery to the base of the urachus (*11*), the vein from the base of the urachus (*12*), the vas deferens (*13*), the testis (*14*), the epididymis (*15*), the artery and vein of the testis (*16*), the fascia of the inguinal canal (*17*), the artery and vein of the leg (*18*), the umbilical artery (*19*), the urachus (*20*), the adrenal gland (*21*), the penis (*22*) and the urethra (*23*).

well formed epididymides and testes. These structures were located near the abdominal openings of the inguinal canals.

The vascular system above the diaphragm was normal. In the posterior abdominal wall the inferior vena cava coursed along the right side of the vertebral column and received a small tributary from the right adrenal gland at the level of the adrenal hilus. A large vein, probably a remnant of vessels taking part in the embryonic subcardinal anastomosis (fig. 2), extended across the aorta and the vertebral column and connected the lower portion of the vena cava (subcardinal vein) with a similar structure on the left. The venous channels coursed downward on each side from this point and may be named subcardinal veins. In their course along the lateral surfaces of the vertebral column they received small tributaries from the muscles of the posterior abdominal wall, the mesentery, the urogenital sinus, the vasa deferentia and the testes. They entered the lower extremity just medial to the inguinal rings, where they became subcutaneous in location and from which point they may be called femoral veins.

The descending aorta entered the abdominal cavity in a typical manner (fig. 2). It gave off three branches just above the level of the adrenal hilus. One short branch extended along the anterior surface of the vertebral column and suggested the fetal sacral artery. The other two longer branches, after supplying the adrenal glands, coursed inferiorly along the lateral aspects of the vertebral column, giving off branches to the muscles of the posterior abdominal wall, the urogenital sinus, the vasa deferentia and the testes. These longer branches, which resembled iliac arteries except in their point of origin, then passed into the lower extremity in close proximity to the femoral veins. As the aorta descended it coursed behind the base of the urogenital sinus and continued upward between the urogenital sinus and the anterior abdominal wall to the umbilicus as the umbilical artery.

The bones of the skull were normal. There were seven cervical vertebrae, to the last of which were attached two very short cervical ribs. The arrangement of the thoracic vertebrae departed from the normal in many respects (fig. 3). A total of ten ribs were present on each side, although their origins were not symmetric. Two ribs were attached to the body of the second thoracic vertebra on the right and one on the left. One rib was attached to the body of the third vertebra, which was small and wedge shaped, the base being situated on the left. Only one rib was attached on each side of the bodies of the fifth and sixth vertebrae, which were fused. A spina bifida occulta involved the eighth and all succeeding vertebrae. No ribs were attached to the twelfth vertebra. The five separate bodies of the lumbar vertebrae showed no uniformity of size, shape, location or axial plane. A thin, slightly concave, cartilaginous body which resembled the fetal sacrum was situated below the last lumbar vertebra, with its longitudinal axis directed anteroposteriorly. Its concave surface was directed inferiorly and was closely applied to the anterosuperior surface of the fused ilia. Between the sacral mass and the lumbar vertebrae on the left was an opening 4 mm. in diameter, through which the lower part of the spinal cord, bending at right angles, passed to the superficial tissues of the back.

No abnormality was seen within the skull. The spinal cord measured 10.2 cm. in length. The spinal nerves appeared to be normal except that those of the lumbar portion of the cord did not form a true cauda equina. As was previously stated, the cord itself passed through the opening between the lumbar portion of the spine and the rudimentary sacrum on the left for 1 cm. into the subcutaneous tissues of the back. The dura continued on as a sac and was attached just under the skin of the nodule noted in the skin of the lumbar region.

The lower end of the vertebral column rested on the anterosuperior margin of the fused ilia. The iliac bones were fused in the midline posteriorly and gave the impression of being one bone (fig. 4). In the line of fusion there was noted a foramen which led into a short channel. The latter passed obliquely downward and divided into two, one opening on the posterior and one on the inferior surface of the fused ilia. Attached to the lower portion of the ilia, but not fused with them, were two pubic bones, which extended downward. At their lower margins they curved posteriorly and came in contact on each side with rudimentary ischial bones. The pubic and ischial bones were not fused but were connected by a

Fig. 3.—Roentgenogram (posterior view). The great variation in size and shape and the symmetric placement of the thoracic and lumbar vertebrae are apparent. The plate resembling a sacrum is seen at the base of the spinal column.

fibrous band. There were well formed but shallow acetabulums located on the lateroposterior surfaces of the innominate bone at the ilioischial junction.

The femurs were well developed (fig. 4) except that their proximal ends were fused. True heads were missing, but the anterior portion of the proximal end of each femur projected into the acetabulum. True trochanteric elevations were also absent. The medial and lateral condyles were present, and the medial aspects of the lower extremity of the femurs were fused. Bilobate patellar facets were located on the posterior surfaces. Closely applied to these facets were two distinct, slightly concave patellas. The tibial bones were well formed throughout. A small cartilaginous mass was found between the incisurae fibulares, and from it a thin

cartilaginous structure, probably representing fused fibular anlages, extended upward. The foot was represented by a quadrangular cartilaginous plate, to which, inferiorly and laterally, were attached in pairs the two phalanges which represented the two toes.

Because of its great variation from the normal, the musculature of the lower extremity is not described in detail. Anteriorly, the muscles were made up of a superficial and a deep group. Similarly arranged muscles were noted on the posterior aspect of the thigh. These muscles originated from the inferior,

Fig. 4.—Anterior view of the bones of the pelvis and the extremity.

posterior and lateral surfaces of the pelvic bones and inserted into the lower ends of the femurs. None of the thigh muscles bridged the knee joint. In the leg the muscles were likewise arranged into a superficial and a deep group, both anteriorly and posteriorly. However, the deeper muscles of the anterior group passed over the ankle joint and inserted into the anterior surfaces of the toes.

The arterial supply of the lower extremity was derived from the two arteries which branched off the aorta and coursed downward just medial to the inguinal region. The vessel which served as the right femoral artery passed deeply between the anterior set of thigh muscles, coming to be placed between the superficial and the deep group. It coursed inferiorly over the knee joint, between the superficial and the deep group of muscles of the lower part of the leg and over

the anterior surface of the foot. The left femoral artery was placed lateral to the femur and coursed inferiorly in a manner similar to that of the right artery except that it was located on the posterior aspect of the extremity. Frequent anastomoses were noted about the knee and ankle.

COMMENT

Monsters of the general category into which the one described falls were first classified by Geoffroy-Saint Hilaire.[1] He assigned them to the class of single monsters, to the order of autosites, to the family of teratomelians and to the genus of symelians. The genus was further divided into three subgroups. The first of these subgroups consisted of symeles, monstrosities whose two legs are almost perfectly united and terminate in a double foot, with the sole on the anterior surface. The second subgroup consisted of uromeles, which are characterized by two incompletely united legs ending in an incomplete single foot, with the sole also on the anterior surface. The third subgroup consisted of sirenomeles, which are characterized by incomplete union of the legs and the absence of a distinct foot.

Förster [2] renamed these subgroups sympus dipus, sympus monopus and sympus apus respectively. Since that time numerous variations and combinations of the original classification have been offered, none of which has proved entirely satisfactory. This inadequate terminology may be due to its derivation from either historic or anatomic sources. It seems that a nomenclature based on anatomic criteria is likely to be unsatisfactory because usually the anatomic abnormalities involve different organs in each case. Heretofore the terminologic emphasis has been placed on the extremity, although it has not been proved that the cause of the abnormalities is lodged there primarily or even that the anomalies of the extremity are of more significance than the changes which are constantly present in the vascular and the genitourinary system. It seems probable, in the light of recent work on such features as chemodifferentiation and organizers, that the causation of the abnormal conditions will have to be sought elsewhere. It seems therefore that a satisfactory nomenclature must await the clarification of the causation of the monsters.

The incidence of sirenomelian monsters is fortunately very low. Proshek [3] stated that monsters with fusion of the lower extremities make

1. Geoffroy-Saint Hilaire, I.: Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux; ouvrage comprenant des recherches sur les caractères, la classification, l'influence physiologique et pathologique, les rapports généraux, les lois et les causes des monstruosités, des, variétés et vices de conformation, ou traité de tératologie, Paris, J. B. Baillière, 1832, vol. 2.

2. Förster, A.: Die Missbildungen des Menschen, systematisch dargestellt, nebst Atlas, Jena, F. Manke, 1860, pt. 1; 1865, pt. 2.

3. Proshek, C. E.: Sympus Dipus: Anatomic Study, Am. J. Obst. & Gynec. **10**:15-35 (July) 1925.

up approximately 1 per cent of those born. Ballantyne [4] found 116 cases reported in the literature. Kampmeier,[5] after an exhaustive study of the literature, added 50 additional cases, and the total number now on record approaches 190.

Kampmeier [5] has tabulated the abnormalities in the examples of this disorder recorded in the literature. Most of the monsters were born at full term, and a few, as that in the case reported here, lived for short periods after birth. The mothers were usually multiparas. Of interest is the fact that monsters were present in 5 sets of twins, in 4 of which the other twin was normal. In the fifth instance the second twin exhibited several congenital anomalies. In 38 of the 52 cases in which the sex was stated the monster was male. Defects in the skull, the face and the neck were occasionally noted. Anomalies of the upper extremity were not infrequent. Defects of the vertebral column, the diaphragm and the upper abdominal organs were common. The external genitalia were defective in 22 cases and entirely absent in 33. In 45 of 54 cases in which this detail was mentioned the anus was missing. The adrenal gland was stated to be abnormal in 14 cases. In all instances there were abnormal coiling of the intestine and abnormalities of the mesenteric relation. The appendix was absent in 2 cases. The colon terminated blindly in 32 cases. The kidneys were normal in only 3 reported cases; they were defective in 28 and absent in 18. The ureters were absent in 23 cases and defective in all the remaining cases. The bladder was absent in 25 cases. The case here reported is apparently the only one in which a well developed patent urethra was present. In all of the cases reported there was a single umbilical artery. The outstanding observation in Kampmeier's résumé of the literature was that abnormalities of the genitourinary and intestinal tracts and the vascular systems of the lower part of the abdomen were as constant as the abnormalities of the lower extremity.

It is not necessary to give an account here of the numerous theories which have been advanced for the causation of sirenomelian monsters. Whatever the initiating factor may be, it is apparent that it exerts its effects very early in fetal life. The formation of the ureters, the aorta and the umbilical arteries, as well as the limbs, is always disturbed in sireniform monsters. The ureteric buds appear first at approximately the 4.5 mm. stage of development, at which time the limb buds also appear. The aortas and the umbilical arteries are still separate at this

4. Ballantyne, J. W.: The Occurrence of a Non-Allantoic or Vitelline Placenta in the Human Subject, Tr. Edinburgh Obst. Soc. **23**:58-81, 1898.

5. Kampmeier, C. F.: On Sireniform Monsters, with a Consideration of the Causation and the Predominance of the Male Sex Among Them, Anat. Rec. **34**: 365-389 (Feb. 25) 1927.

stage. It therefore seems reasonable to infer that the disturbing factor appears not later than this stage and possibly earlier.

Furthermore, in an embryo of this size, all the structures are placed in intimate relation to each other, and any disturbance in the development of one might easily affect the others. Ordinarily the fetal genitourinary system, being connected with the cloacal region, prevents the approximation of the lower portions of the aortas and the umbilical arteries, thus giving rise to the adult form of the vascular pattern of the lower part of the abdomen and the lower extremities. In the specimen which is reported on in this paper there was some interruption of tissue between the base of the urogenital sinus and the anal portion of the cloaca; it might be assumed that such a defect would permit the close approximation of the lower portions of the aortas and the umbilical arteries. When fusion of the aortas occurs under such circumstances, there would be nothing to prevent its becoming complete and resulting in the formation of a single, continuous (aortic-umbilical) artery.

The lower extremity of such monsters, although abnormal in structure, reaches a much higher degree of development than do the vessels of the lower part of the abdomen and the renal-ureteral system. This fact, in conjunction with the speculations already mentioned, warrants the assumption that the primary disturbance involves the region associated with the base of the urogenital sinus. The changes in the limbs, which are frequently disproportionately stressed, are very probably incidental to disturbances more proximally placed.

SUMMARY AND CONCLUSIONS

A sireniform monster is described and the postmortem observations recorded.

The case here reported seems to be the only one in which a well developed, patent urethra was present.

The unsatisfactory nature of the present nomenclature is commented on.

The original disturbance is tentatively placed at the base of the urogenital sinus at or before the 4.5 mm. stage.

An effort is made to explain the occurrence of a single umbilical-aortic artery in such monsters.

Progress in Pediatrics

RENAL HYPERTENSION IN CHILDREN

CLINICOPATHOLOGIC STUDIES

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AND
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Persistent hypertension in children, it is becoming evident, is more common than has been appreciated. Aside from its well recognized occurrence in conjunction with glomerulonephritis, it is apparent that hypertension due to urologic conditions and a variety resembling the so-called essential hypertension of adults also occur. For this reason pediatricians are making more systematic surveys of the arterial blood pressure of children. Since it is evident that much might be done therapeutically in the early stages of hypertension, this tendency is commendable and should be encouraged.

Persistent hypertension in children is practically always associated with renal disease. The relative number of instances in which urologic disabilities are responsible for elevated blood pressure is appreciably greater in the cases of children than in those of adults. Essential hypertension is relatively rare in children. Nevertheless, as Sobel [1] has suggested, transient hypertension in children, for example, that which occurs during emotional strain, which is observed in office and clinic practice may turn out to have an important bearing on the later development of essential hypertension. It is also becoming clear that in children chronic pyelonephritis is a more common cause of hypertension than is chronic glomerulonephritis.[2] In a previous communication one of us (J. K. C.) has already discussed the clinical and therapeutic aspects of juvenile hypertension associated with urologic conditions.[3]

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From the Cardiovascular and Pathology Departments and the Sarah Morris Hospital for Children of Michael Reese Hospital.

1. Sobel, I. P.: So-Called Essential Hypertension in Childhood, Am. J. Dis. Child. **61**:280 (Feb.) 1941.

2. Butler, A. M., and Lanman, T. H.: Examination of the Child with Chronic Pyelonephritis, New England J. Med. **217**:725, 1937.

3. Calvin, J. K.: Hypertension in Children as Related to Urologic Conditions, Urol. & Cutan. Rev. **45**:71, 1941.

Recently, there has been a spurt in investigations on the mechanisms of hypertension which has considerably altered our point of view. It was felt that a survey of the literature, together with a detailed discussion of several interesting cases of juvenile hypertension in which anatomic studies of the kidneys obtained at operation or at necropsy were carried out, might be of value in this connection.

SOURCE OF MATERIAL

For this report on renal hypertension we have selected 6 cases of persistent hypertension in which the patient was admitted to Sarah Morris Hospital for Children of Michael Reese Hospital between the years 1930 and 1941, and one or both kidneys were obtained for study. Four patients came to necropsy; the remaining 2 underwent unilateral nephrectomy and are still living at the time of this report. In all cases the persistence of the hypertension was established by a sufficient number of blood pressure determinations. Cases of chronic glomerulonephritis were excluded, since the association of hypertension with this condition is well known. During this eleven year period autopsy was performed in the cases of 3 children with subacute or chronic glomerulonephritis, in each of which elevated blood pressure was present. Chronic bilateral pyelonephritis was present in 1 instance in addition to the glomerulonephritis. Another of these cases, an instance of subacute glomerulonephritis, was included in our report because of its interesting clinical and pathologic features.

The material will be presented in the form of case reports followed by discussions of some of the principle observations in the light of the more recent experimental and clinical knowledge.

REPORT OF CASES

CASE 1.—*Congenital unilateral renal hypoplasia with nephrosclerosis.*

M. B., a 4½ year old boy, was first seen in Mandel Clinic of Michael Reese Hospital on June 11, 1938. One month previously he had had paroxysmal abdominal pain, and since then his appetite had been poor and he had been losing weight. The past history and the familial history were noncontributory. Physical examination at this time revealed nothing unusual. However, when he returned to the clinic a week later there was a sense of resistance to palpation on the right side of the abdomen. Rectal examination gave negative results. The Wassermann and Kahn reactions of the blood were negative. The erythrocyte count was 4,800,000 and the leukocyte count 16,000 cells per cubic millimeter of blood, with 82 per cent polymorphonuclear leukocytes; the hemoglobin content was 70 per cent, and the nonprotein nitrogen content was 34 mg. per hundred cubic centimeters. Examination of the urine showed a specific gravity ranging between 1.004 and 1.017, albumin 1 plus to 4 plus and an occasional red blood cell and leukocyte.

First Hospitalization.—On July 7, because of continued tenderness on the right side of the abdomen and the loss of 3 pounds (1.3 Kg.) in weight during the

period he had been under observation, the child was admitted to Sarah Morris Hospital for Children.

Physical Examination: The temperature and the pulse and respiratory rates were within normal limits. There was a definite sense of resistance to palpation over the right side of the abdomen, opposite the umbilicus, even when the child was under sedation. The results of the remainder of the physical examination were not remarkable.

Laboratory Examinations: The values for the red blood cell count, the hemoglobin content, the white blood cell count and the nonprotein nitrogen content of the blood were similar to those obtained in the clinic. The cholesterol content of the blood was 202 mg. per hundred cubic centimeters, and the icteric index was 9.

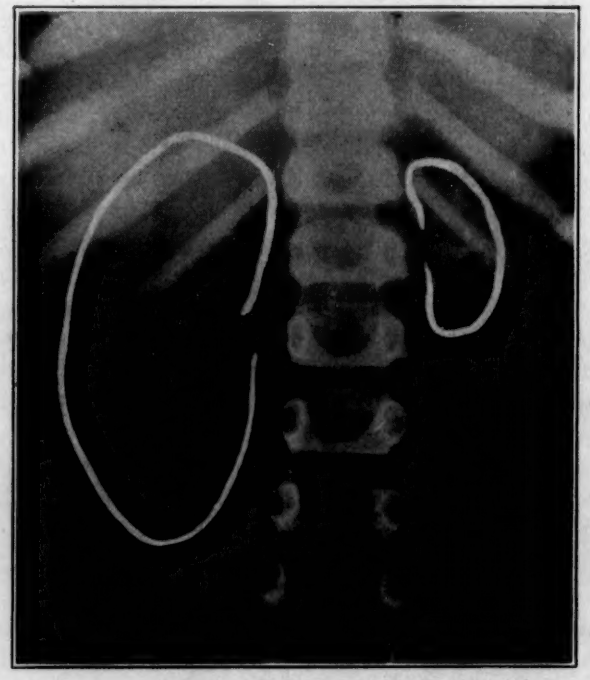

Fig. 1 (case 1).—Intravenous pyelogram, showing hypoplasia of the left kidney and hypertrophy of the right kidney. (The kidneys have been outlined in white ink.)

Examination of the urine showed albumin (up to 1+) and a rare blood cell. One examination of the stools gave positive results for occult blood. Roentgenograms of the gastrointestinal tract were normal. The report on an intravenous urographic examination (fig. 1) was as follows:

"The right renal outline was well visualized and definitely enlarged. There was immediate and excellent concentration on this side. On the left side an ovoid shadow about the size of a large plum could be seen lying in the angle formed by the twelfth rib and the spine. Within it an area of increased density was visualized which had the appearance of a miniature dye-filled renal pelvis and calices."

A retrograde pyelographic examination confirmed the diagnosis of hypoplasia of the left kidney.

Course.—Abdominal pain and tenderness decreased, and the patient was discharged on July 22. He was followed up in the clinic, and during the next month he gained several pounds in weight and no longer complained of abdominal pain.

Second Hospitalization.—On August 29 the child was readmitted to the hospital because of abdominal cramps and occasional episodes of vomiting during the previous week. On this admission he appeared ill.

Physical Examination: The temperature was 98.8 F., and the pulse rate was 128 and the respiratory rate 26 per minute. The arterial blood pressure was 190 mm. of mercury systolic and 140 mm. diastolic. This was the first reading of the blood pressure which was taken, either in the clinic or during the first hospitalization. Examination of the lungs gave negative results. The heart was not enlarged to percussion. There were systolic murmurs over the mitral and aortic areas. Abdominal examination revealed a mass which extended 2 finger-breadths down from the right costal margin and was firm and slightly tender. There was a definite sense of resistance to palpation on the right side of the abdomen.

Ophthalmoscopic Examination: The report on the ophthalmoscopic examination was as follows:

"The disks appear pale and hazy, with indefinite outlines. The central excavation seems to be entirely obliterated. There is moderate edema of the disks. The veins in general appear engorged and tortuous and the arteries narrowed and beaded. Throughout the retina there are enormous areas of exudation and in the macular area a classic star. The picture is that of chronic severe involvement of the vascular supply on a renal basis."

Course: During the next few days the abdominal pain became more severe and the stools were mixed with dark red blood. The temperature rose gradually to 105 F.; there were elevations also of the pulse and respiratory rates. The blood pressure determinations were as follows: 210 systolic and 140 diastolic, 192 systolic and 140 diastolic, 190 systolic and 110 diastolic and 150 systolic and 110 diastolic. The abdomen became markedly distended, but there was no rigidity. The child became stuporous and died on September 4.

Laboratory Data: The results of laboratory studies were as follows: erythrocyte count, 2,500,000 to 2,100,000 cells per cubic millimeter; leukocyte count, 31,000 to 47,000, with 75 per cent polymorphonuclear leukocytes, and hemoglobin content, 60 to 50 per cent. The specific gravity of the urine ranged between 1.002 and 1.010 (the patient received a considerable quantity of fluid parenterally); albumin (1 + to 4 +) was present, and there was an occasional leukocyte on microscopic examination. Examination of the blood showed: nonprotein nitrogen, 31 mg. per hundred cubic centimeters; creatinine, 1.1 mg.; cholesterol, 161 mg., and total plasma proteins, 5.7 Gm.

Clinical Diagnosis.—The clinical diagnoses were: (1) peritonitis, due either to rupture of Meckel's diverticulum or to ulceration of the bowel with perforation, and (2) hypertension due to vascular anomaly of a hypoplastic kidney.

Necropsy.—Gross Examination: The peritoneal cavity contained a small amount of slightly turbid fluid. The small intestine was arranged in somewhat parallel distended loops which were plastered together by a fragile but binding fibrinous exudate. The adhesions were separated readily. The involved bowel was discolored with patches of purple and reddish blue and consisted of a portion of the

distal part of the jejunum and the portion of the ileum extending to within 35 cm. of the ileocecal valve. The mesenteric vessels showed no gross changes. The mucosa of the involved portions of the jejunum and ileum was reddish blue and granular and was covered by an irregular, incomplete gray membrane which was readily scraped away.

The right kidney weighed 90 Gm. (normal, 60 Gm.). The capsule stripped readily to reveal a pale pinkish tan, smooth surface. Resistance to section was normal; the cortex was pale and tannish, with pinkish tan pyramids. The ratio of the mass of the cortex to that of the medulla was about 2:3. The pelvis and the ureter showed no changes. The left kidney weighed only 14 Gm. The external surface was lobulated, and several depressed, scarred areas were present. The capsule stripped fairly readily. The cut surfaces were grayish red. The demarcation of cortex and medulla was poor, but the ratio of the mass of the cortex to that of the medulla was about 1:3. The pelvis was smooth and of about normal size. The ureter showed no changes. The urinary bladder was normal.

The heart weighed 125 Gm. (normal, 85 Gm.). The left ventricle was markedly hypertrophied. The liver was moderately enlarged, and the architecture on section was somewhat indistinct. The brain was pale, and at the base of the right frontal lobe there was a small, irregularly shaped cyst containing clear brownish fluid. The remaining organs showed no gross changes.

Histologic Examination: Right Kidney: The larger and the medium-sized arteries showed slight to moderate intimal hyperplasia with splitting and reduplication of the elastica interna. The smaller arteries and the arterioles showed moderate thickening of the walls, with increase of cells and partial obliteration of the lumen. The glomeruli for the most part were unchanged. A few, however, were partially or completely sclerosed. The convoluted tubules were lined by swollen granular epithelium, and occasional desquamated epithelial cells were found in the lumens. The interstitial tissue was slightly increased in focal areas, but there was no infiltration with inflammatory cells. The renal pelvis showed no changes.

Left Kidney: The striking changes were found in those portions which were depressed grossly (fig. 2). These areas were sharply demarcated from the remaining portions of the parenchyma, which histologically were similar to the parenchyma of the right kidney. The arterial changes in the scarred areas dominated the picture. The larger and the medium-sized arteries showed marked splitting and reduplication of the elastica interna, often with considerable hyperplasia of the subintimal connective tissue. The lumens were markedly reduced, and even completely obliterated in some instances. Surrounding these vessels were areas of fibrosis. The smaller arteries and the arterioles showed marked hypertrophy of the media in addition to the hyperplasia of the elastic and connective tissue of the intima. Most of these vessels showed practically complete obliteration of the lumen. The glomeruli were completely sclerosed and were made out only with difficulty. Most of the tubules were small and collapsed, with little or no lumen visible. Some contained a homogeneous colloid material. Occasional cystic or slitlike cavities were seen in the cortex. Although the stroma was very dense, there were no diffuse or local collections of inflammatory cells. The renal pelvis presented no evidence of recent or chronic inflammation.

Small Intestine (sections from the involved portion of the ileum): The mucosa was largely denuded, and only occasional remnants of glandular structures remained. The submucosa was covered with a deeply eosinophilic, markedly fragmented and ragged coat of fibrin and debris, infiltrated with numerous polymorphonuclear leukocytes and occasional lymphocytes and macrophages. The

capillaries of the submucosa were tremendously engorged, and there was marked edema, with some areas of hemorrhage. The submucosa was infiltrated with many inflammatory cells. The small arteries and the arterioles showed moderate to marked thickening of their walls, some of which were invaded by polymorphonuclear leukocytes. Occasional arterioles and veins were plugged with recent thrombi. There was a deposit of fibrin on the serosal surface, in which many polymorphonuclear leukocytes were enmeshed.

Remainder of the Gastrointestinal Tract, Pancreas, Spleen, Liver and Voluntary Muscle: These structures showed slight to moderate arteriolosclerosis. In the liver there was also an increase of fibrous connective tissue in the portal areas, which at times was infiltrated with lymphocytes.

Fig. 2 (case 1).—Hypoplastic left kidney. Note the sharp demarcation between the scarred portion of the kidney (on the right) and the practically normal renal parenchyma (on the left). The arteries leading to the atrophic portion are surrounded by dense fibrous tissue and show marked narrowing of the lumen. The arteries supplying the relatively uninvolved portion show little change. (Orcein elastic tissue stain; × 38.)

Heart: The muscle fibers were hypertrophied; there was slight to moderate sclerosis of the coronary arteries.

Brain: There was moderate arteriolosclerosis in places, and the cyst noted grossly proved to be an area of encephalomalacia with rather recent hemorrhage, many macrophages filled with blood pigment being present.

Pathologic Diagnoses.—The pathologic diagnoses were: congenital hypoplasia of the left kidney with arteriosclerotic scars; compensatory hypertrophy of the

right kidney; bilateral nephrosclerosis of the arteriolar variety; arteriolosclerosis involving the small intestine, the adrenal capsule, the pancreas, the spleen, the liver, the brain and the voluntary muscles; hypertrophy of the heart, especially of the left ventricle; acute pseudomembranous enteritis; acute fibrinous peritonitis, and early periportal fibrosis.

Comment.—In this case of unilateral renal hypoplasia with hypertension the predominant symptom was abdominal pain, and death was due to enteritis, peritonitis and hemorrhage into the bowel. A review of the literature shows a definite relation between hypertension and complaints referable to the gastrointestinal tract and pathologic changes therein. Guild, Kindell and Gibson [4] reported the cases of 2 girls, each aged 9 years, with arteriosclerosis and marked hypertension. Abdominal symptoms, pain and melena, were prominent in both and were directly or indirectly the immediately precipitating cause of death. The pathologic report of diphtheritic and ulcerative ileitis in the first case is of interest because of its close resemblance to the condition present in ours. The cases of 3 children with malignant hypertension, in 1 of which necropsy was performed, were reported by Schwarz.[5] The chief complaint in each was marked abdominal pain. In case 2 autopsy revealed acute intussusception involving the ileum, but the arteries and veins leading to the gangrenous areas were apparently normal. Weiss and Parker [6] reported the case (case 11) of a 12 year old girl with marked hypertension who complained of headache, abdominal pain, nausea and vomiting of one month's duration. There were abdominal tenderness and progressively increasing abdominal discomfort. Necropsy revealed that death was caused by infarction of the ileum.

Why the ileum should be the selected site of damage, although usually the remainder of the gastrointestinal tract also shows arteriolosclerosis, is not known.

The other striking feature in our case is the congenital hypoplasia of one kidney (fig. 1). Ask-Upmark [7] analyzed 20 cases of juvenile malignant nephrosclerosis collected from the literature and concluded that the simultaneous presence of renal anomalies and malignant nephrosclerosis was not coincidental. He reported 6 cases of juvenile malignant nephrosclerosis, in 5 of which there were renal anomalies consisting of the triad of (*a*) unilateral renal hypoplasia, (*b*) lobulation of the

4. Guild, H. G.; Kindell, F. B., and Gibson, T. A.: Arteriosclerosis in Childhood, with a Report of Two Cases, Bull. Johns Hopkins Hosp. **62**:159, 1938.

5. Schwarz, H.: Kidney Diseases in Infants and Children: II. Malignant Hypertension Nephritis; Primary Sclerotic Kidney (Schrumpfniere), Am. J. Dis. Child. **27**:233 (March) 1924.

6. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

7. Ask-Upmark, E.: Juvenile Malignant Nephrosclerosis and Maldevelopment of the Kidneys, Acta path. et microbiol. Scandinav. **6**:383, 1929.

hypoplastic kidney by a horizontal groove, approximately in the middle of the kidney, and (*c*) diverticula or recesses coming off the renal pelvis, which were unassociated with a papilla or pyramid. Between the vertex of the diverticulum and the surface of the kidney, corresponding to the horizontal groove, there was found a small, somewhat fibrous bridge of parenchyma, demarcated from the rest of the kidney. Microscopically this region showed marked sclerosis of the arteries and arterioles; no glomeruli or their remains were visible, typical tubules were absent and usually many cystic spaces lined by flat epithelium were present. This complex of anomalies was usually confined to females and was not often associated with other disease of the kidneys. De Takáts and Scupham [8] reported the case (case 3) of a 7 year old girl with marked hypertension in which the observations were similar to those in the foregoing cases. Other instances of hypertension and juvenile nephrosclerosis associated with unilateral renal hypoplasia were reported by Røjel and Søbye [9] and by Clark.[10] Autopsy in the previously mentioned case 11 of Weiss and Parker [6] showed a left kidney which weighed only 10 Gm., had a small renal artery and microscopically showed chronic pyelonephritis. It is likely that this kidney was hypoplastic.

There appears to be a definite relation between unilateral congenital hypoplasia of the kidney and the consequent development of hypertension. This does not imply, however, that small kidneys per se necessarily lead to hypertension, for arterial hypertension is uncommon in patients with renal dwarfism and renal rickets associated with congenital dilatation of the urinary tract and small, fibrotic kidneys.[11] This may be due to the fact that in cases of the latter type the arterial changes are not pronounced.

It may be that the congenitally small kidney in our case was the original source of the pressor substance which led to the production of hypertension. Possibly one or more of the branches of the main renal artery were defective in formation and this abnormality led to progressively increasing arteriosclerosis, with gradual narrowing of the lumens and "ischemia" and atrophy of those portions of the renal parenchyma supplied by them (fig. 2). The generalized bilateral renal arterio-

8. de Takáts, G., and Scupham, G. W.: Revascularization of the Ischemic Kidney, Arch. Surg. **41**:1394 (Dec.) 1940.

9. Røjel, K., and Søbye, P.: Juvenile Nephrosclerosis in Connection with Anomalies of Development; Case, Nord. med. (Hospitalstid.) **6**:1061, 1940.

10. Clark, H. C.: Hypertension in Early Childhood, Am. J. Dis. Child. **59**: 353 (Feb.) 1940.

11. Leiter, L.: Unusual Hypertensive Renal Disease: I. Occlusion of Renal Arteries (Goldblatt Hypertension); II. Anomalies of Urinary Tract, J. A. M. A. **111**:507 (Aug. 6) 1938. Ellis, A., and Evans, H.: Renal Dwarfism, Quart. J. Med. **2**:231, 1933. Hamperl, H., and Wallis, K.: Ueber renale Zwergwuchs ohne und mit (renaler) Rachitis, Ergebn. d. inn. Med. u. Kinderh. **45**:589, 1933.

sclerosis and arteriolosclerosis in our case may have been secondary to such systemic hypertension, which in turn would have increased and perpetuated the renal "ischemia" and would have resulted in the marked hypertension. Coplin [12] stated that there is a type of renal anomaly, consisting of unilateral renal hypoplasia and dysplasia, which predisposes to or renders inevitable some form of nephritis and that this congenital abnormality is probably due primarily to a defect in arteriogenesis which necessarily occurs early in the evolution of the organ.

It has been shown in cases reported by Butler,[13] Leadbetter and Burkland,[14] Howard, Forbes and Lipscomb [15] and Kennedy, Barker and Walters [16] that when unilateral renal disease apparently is the source of the hypertension removal of the diseased kidney will cause a fall of the blood pressure to normal levels. However, Benjamin and Ratner [17] recently reported the case of a 6 year old boy who had hypertension associated with pronounced atrophic pyelonephritis and marked functional impairment limited to one kidney, the opposite kidney being normal, in which unilateral nephrectomy was not followed by a decline of either the systolic or the diastolic blood pressure. Furthermore, Schroeder and Fish [18] emphasized that when the hypertension has existed for a long time and there is vascular involvement of the opposite kidney unilateral nephrectomy will be of no avail in lowering the blood pressure.

Thus, even if the hypoplastic kidney had been removed while our patient was under observation it is doubtful that the hypertension would have subsided, since the vascular changes in the hypertrophied kidney were probably already present. However, had nephrectomy been per-

12. Coplin, W. M. L.: Unilateral Renal Hypoplasia and Dysplasia Due to Defective Anteriogenesis: Relation to So-Called Hypogenetic Nephritis, Am. J. M. Sc. **153**:381, 1917.

13. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889, 1937.

14. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611, 1938.

15. Howard, T. L.; Forbes, R. P., and Lipscomb, W. R.: Aneurysm of the Left Renal Artery in a Child Five Years Old with Persistent Hypertension, J. Urol. **44**:808, 1940.

16. Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in a Child: Cure Following Nephrectomy, Am. J. Dis. Child. **61**:128 (Jan.) 1941.

17. Benjamin, B., and Ratner, M.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Occurrence in a Child in Whom No Decrease of Blood Pressure Followed Nephrectomy, Am. J. Dis. Child. **61**:1051 (May) 1941.

18. Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, Am. J. M. Sc. **199**:601, 1940.

formed at an earlier date, it is possible that the later events might have been averted.

CASE 2.—*Chronic bilateral pyelonephritis with contracted kidneys.*

A. C., a 6 year old white boy, was admitted to Sarah Morris Hospital for Children on May 5, 1930. Since the age of 8 months the child had been in poor health. At that time he had lost some weight and was treated by a physician for "rickets." At 3 years of age he was listless and underweight and often had attacks of "bronchitis." Five months before admission to this hospital he had generalized convulsions and was in coma for five days (at another hospital). At the same time he had urinary retention and had to be catheterized for three weeks. He remained in that hospital for one month and left improved. Three weeks after returning home he had an infection of the upper respiratory tract, and two days later he had convulsions, puffiness of the eyelids and some swelling of the face. He was taken back to the hospital, where he remained for twelve days, and then returned home. Soon after he again had convulsions.

Physical Examination.—Physical examination on admission to Sarah Morris Hospital for Children showed that he was undersized and very pale. He was incapable of standing and was mentally retarded. The skin was flabby, the hair silken and the gums tender and swollen. The teeth were carious and the tonsils enlarged. Bilateral cervical lymphadenopathy was present. There were depressions of the left seventh, eighth and ninth ribs in the anterior axillary line. The heart was not enlarged to percussion, but systolic murmurs were heard at the apex and at the base. There were 6 digits on each foot. There were no other abnormalities.

Laboratory Data.—The Wassermann and Kahn reactions of the blood were negative. The erythrocyte count was 1,650,000 and the leukocyte count 8,000 cells per cubic millimeter of blood; the hemoglobin content was 45 per cent. Examination of the blood showed: nonprotein nitrogen, 95 mg. per hundred cubic centimeters, and creatinine-cholesterol, 180 mg. Examination of the urine showed albumin (1 + to 2 +) and an occasional leukocyte.

Blood Pressure.—The blood pressure on admission was 154 systolic and 90 diastolic, and afterward it ranged between 146 systolic and 162 diastolic and 86 systolic and 90 diastolic.

Course.—During hospitalization the child had twitching of the hands and face followed by generalized convulsions. Occasionally he had watery stools. The temperature varied between 99.6 and 101.6 F. He died on May 19 after having generalized convulsions.

Clinical Diagnosis.—The clinical diagnoses were (1) chronic glomerulonephritis with uremia and (2) hypertension.

Necropsy.—Gross Examination: The kidneys were very small; together they weighed 32 Gm. (normal, 68 Gm. each). Each organ measured 1 by 2 by 4 cm. The capsules stripped with difficulty and revealed reddish gray granular surfaces which were very irregular because of the presence of numerous depressions between which were numerous small cysts filled with clear fluid. Scattered over the surface were lighter, slightly raised nodules about 2 mm. in diameter. On section there was no demarcation between the cortex and the medulla. The thickness of the parenchyma was less than 1 cm. The pelves, the ureters, and the urinary bladder appeared normal, with the exception of marked pallor of the mucosa of the bladder.

The heart was markedly enlarged. The mucosa of the lower part of the ileum and the cecum was moderately hyperemic and was covered by an abundant amount of catarrhal secretion. The remaining organs showed no gross changes.

Histologic Examination: The kidneys were characterized by a marked increase in connective tissue, which was infiltrated with numerous lymphocytes and occasional plasma cells, eosinophils and polymorphonuclear leukocytes. The glomeruli were decreased in number and showed varying degrees of hyalinization. Some glomeruli were definitely larger than normal and showed an increase in nuclei. Periglomerular fibrosis was frequently present. The tubules varied in size and content; in the denser, scarred areas they were atrophic and contained hyaline casts, while in other areas, especially those corresponding to the nodular areas seen grossly, they were markedly dilated and were empty or contained eosinophilic granular material with a few desquamated lining cells and leukocytes. The renal pelvis was thickened, as the result of considerable increase in dense connective tissue, which was moderately infiltrated with lymphocytes. The arteries showed moderate hyperplasia of the intima and the media, with moderate encroachment on the lumen. The arterioles likewise showed moderate thickening of the walls as the result of concentric proliferation of cells.

Pathologic Diagnosis.—The pathologic diagnoses were chronic bilateral pyelonephritis (with contracted kidneys), hypertrophy of the heart and moderate catarrhal enteritis.

Comment.—This child with renal hypertension and contracted kidneys died in uremia. It is often difficult and frequently impossible to make an accurate differential clinical diagnosis between chronic glomerulonephritis and chronic pyelonephritis in cases such as this one, in which the patient is first seen in the terminal stages of the disease. However, such differentiation is important, because chronic pyelonephritis may be curable early in its course by means of chemotherapy and the relief of urinary stasis if present. Some of the differential points may be mentioned. During the course of chronic pyelonephritis there are often recurrent acute febrile exacerbations with pyuria and bacilluria. Only cultures of the urine repeatedly negative for pus and bacilli tend to rule out active pyelonephritis. Late in the course of pyelonephritis the active infection may disappear, so that leukocytes or bacteria may not be present in the urine. The diagnosis, however, can often be made on the basis of a history of acute episodes or by study of intravenous and retrograde pyelograms, which may show distortion, flattening and moderate dilatation of the ureter and the pelvis.

The generally held impression that the majority of children who die in uremia (with or without hypertension) have glomerulonephritis appears to be without foundation. Butler and Lanman [2] after studying over 2,000 reports of autopsies on children found that only 3 patients who died of uremia had chronic glomerulonephritis, while 26 other such patients had chronic pyelonephritis. They emphasized that chronic pyelonephritis is the commonest cause of chronic renal insufficiency in infancy and childhood. Butler [13] reviewed the cases of 15 children

between 3 and 11 years of age in which chronic pyelonephritis was observed at autopsy. In 8 of these in which adequate blood pressure readings were taken definite elevation of both the systolic and the diastolic pressures was present. He also reported on 9 patients with pyelonephritis and hypertension who were still living at the time of the report. He concluded that chronic pyelonephritis with hypertension may exist over a period of years before there is an appreciable diminution of renal function. Weiss and Parker [6] stated that chronic pyelonephritis with small kidneys occurs most frequently in young patients, that is, in those below the age of 30 years. All of their series of patients died in uremia. All, except possibly 1, of the 16 patients had moderate or severe hypertension. Necrotizing arteriolitis occurred in about one half of the cases in which severe hypertension was combined with uremia.

The renal abnormalities in our case can adequately explain the clinical course. The patient apparently had long-standing bilateral pyelonephritis, which over a period caused so much destruction of the renal parenchyma that death resulted from renal insufficiency. The pyelonephritic process also involved the renal arterial system, causing moderate narrowing of the lumens and consequent hypertension.

CASE 3.—*Chronic bilateral pyelonephritis with arteriolonecrosis.*

E. G., a 9 year old white girl, was admitted to Sarah Morris Hospital for Children on June 20, 1938. Four hours before admission she had had an attack of vomiting followed by clonic movements on the right side, nystagmus and semistupor. Three such attacks occurred in rapid sequence soon after admission and were controlled by intramuscular injections of sodium amytal and 25 per cent magnesium sulfate. Three years before she had had scarlet fever complicated by suppurative otitis media. Her urine at that time was reported as normal. For the past few years she had had a poor appetite. Headaches were frequent, and she had remained home from school for the last five weeks of the term because they were becoming more severe.

First Hospitalization.—Physical Examination: Physical examination on admission revealed a thin child who was semistuporous and showed twitching of the right arm and leg; nystagmus was present. Neurologic examination showed no definite localizing signs. Examination of the eyegrounds showed marked blurring and mushrooming of the optic nerve borders, moderate elevation and haziness of the optic nerve margins and many fresh hemorrhages and exudates in the retinas. The heart was moderately enlarged to the left, and a soft systolic murmur was present at the apex. The aortic second sound was accentuated. The blood pressure, which was the same in the upper and in the lower extremities, was 260 systolic and 200 diastolic. The temperature and the pulse and respiratory rates were within normal limits. During the six days the child remained in the hospital there were no further convulsive seizures. The blood pressure remained elevated; the systolic pressure ranged from 245 to 260 and the diastolic pressure was persistently 200.

Laboratory Data: The Wassermann and Kahn reactions of the blood were negative. The hemoglobin content was 70 per cent; the erythrocytes numbered 4,200,000 and the leukocytes 14,150 per cubic millimeter of blood, with a normal

differential count. The specific gravity of the urine varied between 1.002 and 1.010 during a concentration and dilution test; examination of the urine showed albumin (1+ to 3+), a few leukocytes and an occasional hyaline cast. In a phenolsulfonphthalein test 15 per cent of the dye was excreted in one hour and 32 per cent in six and one-half hours. Examination of the spinal fluid revealed a pressure of 350 mm. of water, a total protein content of 33 mg. per hundred cubic centimeters, a negative reaction to the Pandy test and no cells.

Subsequent Laboratory Data.—Soon afterward the child was admitted to another hospital, where the following data were obtained: urea, 86 mg. per hundred cubic centimeters of blood, and creatinine, 1.7 mg. Examination of the urine showed an occasional red blood cell and many leukocytes; culture revealed the presence of many colon bacilli. After the administration of sulfanilamide a culture of the urine was sterile. In a phenolsulfonphthalein test there was 40 per cent excretion of the dye in two hours. After the administration of pentothal sodium the minimum blood pressure was 130 systolic and 110 diastolic.

Second Hospitalization.—The child reentered Sarah Morris Hospital for Children on July 22, because of another convulsive seizure. The results of a physical examination were similar to those obtained on the first admission. The blood pressure was 190 systolic and 140 diastolic. A roentgenogram and a fluoroscopic examination of the chest showed enlargement of the left ventricle. The level of nonprotein nitrogen in the blood was 53 mg. per hundred cubic centimeters, and a renal concentration and dilution test showed that the specific gravity of the urine varied between 1.001 and 1.005. She was discharged on July 27 but returned one week later with a history of severe headache for twenty-four hours and diarrhea, cramps in the lower part of the abdomen and vomiting. The patient was semistuporous, and there were nystagmoid movements of the eyes. Ophthalmoscopic examination revealed old and recent retinal hemorrhages, arteriovenous nicking and papilledema. There was also weakness of the right side of the face. The blood pressure was 270 systolic and 140 diastolic. Death occurred the following morning.

Clinical Diagnosis.—The clinical diagnosis was malignant nephrosclerosis with hypertensive encephalopathy.

Necropsy.—Gross Examination: The kidneys together weighed 120 Gm. (normal, about 82 Gm. each). The right kidney weighed 67 Gm. and measured 6.5 by 4 by 2 cm., and the left weighed 53 Gm. and measured approximately the same. The capsule stripped easily from some portions but was tightly adherent to other parts of the surface. The renal surfaces consisted of a base of deep purple smooth tissue on which were superimposed fine to moderately coarse lobules, ranging in size from that of a pinhead to that of a pea. These granulations were pinkish gray, glistening and firm. Pinpoint hemorrhages were scattered over the surface. Across the middle third of each kidney a depressed pinkish gray scar extended, striated transversely. Over these areas the capsule was adherent. Cut surfaces revealed fairly distinct demarcation between the cortex and the medulla and the presence of small depressed areas of fibrous tissue. The pelves were not dilated. The mucosa of the ureters was smooth and glistening. The urinary bladder appeared large in relation to the size of the other organs. Its mucosa was thickened and edematous. In the region of the trigone there were several small hemorrhagic areas.

The heart weighed 200 Gm. (normal, 115 Gm.) and appeared globular. The left ventricular wall was 1.4 cm., thick while the right ventricular wall measured 0.3 cm. in thickness. The remaining organs showed no gross changes.

Histologic Examination: Kidneys: The sections as a whole showed a great deal of scarring. The scar tissue was not arranged in a definite radiating pattern but was scattered throughout the sections and showed varying degrees of density. The denser areas were markedly infiltrated with numerous lymphocytes and a lesser number of plasma cells. In some places there were focal collections of lymphocytes resembling lymphoid nodules. The tubules were atrophic and contained hyaline casts. The glomeruli were transformed for the most part into completely hyalinized balls; a few were only partially sclerosed, and those showed pericapsular fibrosis. The vascular changes were outstanding; the arteries showed a marked increase in the subintimal connective tissue, and there was often reduplication of the internal elastic membrane and occasionally definite medial hypertrophy. The lumens were usually partially or even completely obliterated. The arterioles had markedly thickened walls as a result of the concentric proliferation of cells, and there was a varying degree of encroachment on their lumens. In adjacent areas other changes

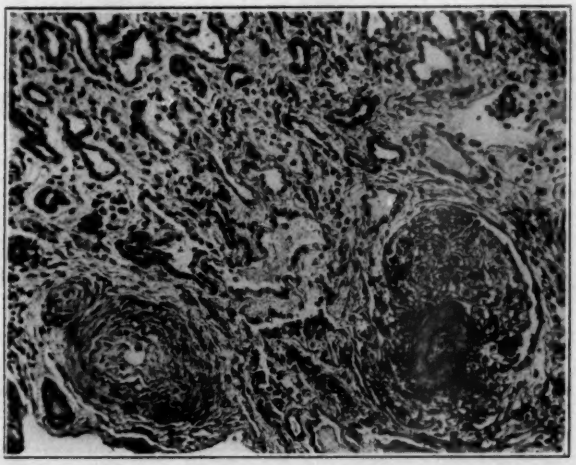

Fig. 3 (case 3).—Necrosis of a glomerular arteriole. On the left are seen an arteriole and a small artery which show practically complete obliteration of the lumen. (Hematoxylin-eosin stain; × 110.)

were noted. There were much less scarring and less cellular infiltration of the stroma. The tubules were much larger, some showing evidence of regeneration; other tubules were markedly dilated, and their lining cells appeared granular or vacuolated, their nuclei were pyknotic or absent and their lumens contained desquamated lining cells, occasional polymorphonuclear leukocytes and a homogeneous eosinophilic material. The glomeruli varied in their state of preservation; some were atrophic with partial hyalinization of the tufts, others appeared normal in size and some were hypertrophied. Some were characterized by complete necrosis of one or more tufts, and frequently the vasa afferentia leading into such glomeruli showed arteriolonecrosis (fig. 3). The walls of such arterioles were smudgy and indefinite in outline, while the nuclei showed karyorrhexis or pyknosis or were completely absent. Occasionally there was hemorrhage into the vessel wall. Polymorphonuclear infiltration of the vessel wall was present only rarely. The remaining arterioles showed slight to moderate arteriolosclerosis. The renal pelvis was thickened and showed moderate infiltration with lymphocytes.

Urinary Bladder: There was considerable infiltration with lymphocytes in the tissues beneath the mucosa.

Pancreas, Adrenal Glands and Spleen: These structures showed slight to moderate arteriolosclerosis.

Pathologic Diagnosis.—The pathologic diagnoses were chronic bilateral pyelonephritis with scar formation; arteriolonecrosis of the kidneys (malignant nephrosclerosis); arteriolosclerosis of the pancreas, the adrenal glands and the spleen; hypertrophy of the heart, especially of the left ventricle, and chronic cystitis.

Comment.—Although bilateral pyelonephritic scars were present in this case of marked hypertension the kidneys had not contracted to the same degree as those in case 2. However, in the present instance the arterial changes were much more marked and accounted for the severe hypertension; death was due to the consequences of the prolonged hypertension rather than to uremia. Also in contrast to the condition in case 2 was the presence of renal arteriolonecrosis. Weiss and Parker [6] reported that in 8 of 19 cases of pyelonephritis with severe hypertension necrotizing arteriolitis was present in addition to the productive endarteritis and hyperplastic arteriolosclerosis.

Goldblatt [19] as a result of his studies on experimental hypertension in dogs expressed the opinion that elevation of the arterial blood pressure (a mechanical factor) and renal insufficiency (a humoral factor) at least are necessary for the development of arteriolonecrosis. It is interesting that the malignant phase of hypertension in his dogs was characterized by terminal renal insufficiency and the development of petechial and larger hemorrhages in many internal organs, but the kidneys were not involved because the clamps put on the renal arteries (for the production of hypertension) caused a decreased pressure distal to them.

However, Wilson and Byrom [20] produced sustained hypertension in rats by partial occlusion of one renal artery, and necrotizing arteriolar changes were often present in the opposite kidney in addition to those in other viscera. Since only one kidney was operated on, renal insufficiency did not appear to be a likely factor in the production of the necrotizing lesions; in support of this was the absence of nitrogen retention in these animals. Since these lesions did not occur in the clamped kidney, they expressed the belief that the production of the lesions is related in some way to the increase in intraarterial tension from which the ischemic kidney is protected by the clip on the renal artery, and also that the determining factor is probably a sudden strain imposed on the vessel wall by the combination of severe vasoconstriction and the resultant rise in blood pressure. This could presumably produce

19. Goldblatt, H.: Studies on Experimental Hypertension: The Production of Malignant Phase of Hypertension, J. Exper. Med. **67**:809, 1938.

20. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension: Experimental Evidence, Lancet **1**:136, 1939.

vascular necrosis, which in the case of a gradually rising pressure might be protected by the development of compensatory hypertrophy of the arterial wall.

The renal arteriolonecrosis in our case, we believe, was due to a combination of marked hypertension and renal insufficiency. Even though the latter component did not result in a condition approaching uremia, that some degree of insufficiency was present was evidenced by the nonprotein nitrogen content of the blood (53 mg. per hundred cubic centimeters), the results of urine concentration studies (specific gravity ranging between 1.001 and 1.005) and the excretion of phenolsulfonphthalein (less than 40 per cent in two hours). The necrotizing lesions occurred in those renal vessels with the least arteriolosclerosis rather than in those showing marked vascular changes with complete or practically complete closure of the lumens (fig. 3). This serves to emphasize that those vessels protected from the full force of the elevated blood pressure will not show necrotizing lesions. Unlike the condition in the experimental studies, there was no arteriolonecrosis in other viscera. This is similar to the experience of Weiss and Parker,[6] who stated that in their group of cases of pyelonephritis and severe hypertension vascular changes in other organs were for the most part absent or of only mild degree. The changes were rarely of the proliferative type, and, in addition, the arteriolar necrosis in other organs was comparatively rare. However, Rubin and Rapoport [21] stated that in contrast to the adult the child with chronic pyelonephritis and hypertension often has diffuse arteriolosclerosis.

This case illustrates clearly the results of neglected pyelonephritis. Even though the infection of the urinary tract was finally cleared up, extensive damage to the renal vasculature and parenchyma had already been done.

CASE 4.—*Bilateral hydronephrosis with chronic pyelonephritis.*

B. L., a 13 year old white girl, was admitted to Sarah Morris Hospital for Children on May 17, 1940 with a history of headache, pain in the eyes with blurring of vision, nausea and vomiting, nocturia and increasing weakness, all of approximately six months' duration; she had lost 18 pounds (8.2 Kg.) in weight. She had scarlet fever at the age of 6 years; otherwise her past history was noncontributory.

First Hospitalization.—Physical Examination: Examination of the fundi revealed that the optic disks were swollen and blurred, the arteries narrowed and the veins engorged and tortuous and that there were extensive exudates and hemorrhages throughout the retina. There were star-shaped exudates in the macular areas. The heart was enlarged to the left, and the aortic second sound was extremely loud. The blood pressure in the arms was 220 systolic and 185 diastolic and in the legs 250 systolic and 195 diastolic.

21. Rubin, M. I., and Rapoport, M.: Arteriosclerosis, Hypertension and Cerebral Atrophy in an Infant, J. Pediat. **18**:643, 1941.

Laboratory Data: The Wassermann and Kahn reactions of the blood were negative. The red cells numbered 4,800,000 per cubic millimeter of blood and the white cells 13,000 to 26,000, with 80 to 84 per cent polymorphonuclear leukocytes; the hemoglobin content was 60 per cent. Examination of the urine showed a specific gravity ranging between 1.006 and 1.012 (determined by a concentration and dilution test), albumin (2 + to 3 +), many leukocytes and an occasional red blood cell. Culture of the urine revealed the presence of hemolytic streptococci. In a phenolsulfonphthalein test 5 per cent of the dye was excreted in thirty minutes and less than 30 per cent in five and one-half hours. The urea clearance was 24 per cent of the normal average. The nonprotein nitrogen content of the blood varied between 45 and 58 mg. per hundred cubic centimeters and on one occasion was 80 mg. The level of creatinine was 1.6 to 2.8 mg. and that of uric acid 4.3 to 6.6 mg. per hundred cubic centimeters of blood. Intravenous urograms, though the concentration of the dye material was poor, revealed bilateral enlargement of the calices and dilatation of the left ureter; the right ureter was not visualized. A cystoscopic examination (performed by Dr. A. Jones) revealed enormous dilatation of the bladder with considerable trabeculation, dilatation of the ureteral orifices and an obstruction at the neck which resembled the middle lobe of a prostate gland. The obstruction was fulgurated and a catheter left in the urethra for a week. The hemolytic streptococcic infection had previously been eradicated with sulfanilamide.

Course: The blood pressure fell to 150 systolic and 104 diastolic during the next few weeks. The patient was discharged on July 14 and was followed up in the clinic, where examination revealed that the blood pressure had returned to its previous high levels.

Second Hospitalization.—She was readmitted to the hospital on Jan. 28, 1941, with the complaints of return of the headaches and increasing dyspnea on slight exertion. The results of physical examination were similar to those obtained on her first admission. The blood pressure was 250 systolic and 160 diastolic.

Laboratory Data: The erythrocytes numbered 3,000,000 and the leukocytes 8,000 per cubic millimeter of blood; the hemoglobin content was 40 per cent. Examination of the urine showed a specific gravity ranging between 1.006 and 1.010, albumin (3+) and numerous leukocytes and red blood cells. A culture of the urine was sterile. Less than 20 per cent of the phenolsulfonphthalein injected in a test was excreted in two hours. The retrograde pyelograms revealed a considerable degree of bilateral hydronephrosis, most marked on the left side (fig. 4). Both of the ureters were tortuous and markedly dilated at the ureterovesical junction. There had been definite progression in the bilateral hydronephrosis and hydroureters since the previous hospitalization.

Operations: Bilateral nephrostomy was carried out on February 14 by Dr. H. C. Rolnick, because a cystoscopic examination had revealed no definite cause for the increasing hydronephrosis. The right kidney was small, soft and saclike; it was bound down to surrounding structures by adhesions. The left kidney was larger than the right and firmer. Mushroom catheters were placed in the renal pelves. A phenolsulfonphthalein test on March 5 showed less than 5 per cent excretion of the dye on the left side in an hour and practically no excretion on the right. On March 13 right partial ureteronephrectomy was performed by Dr. Rolnick. Urine from the catheter in the pelvis of the left kidney varied in specific gravity from 1.006 to 1.024 and contained albumin (2 + to 3 +), and many leukocytes and red blood cells. After both the bilateral nephrostomy and the right ureteronephrectomy, the systolic and diastolic blood pressures temporarily showed

a decline, but they soon returned to the previous markedly hypertensive levels. The nonprotein nitrogen content of the blood fluctuated between 40 and 94 mg. per hundred cubic centimeters. An electrocardiogram showed left ventricular preponderance.

On April 11 the urine from the catheter in the left renal pelvis became grossly bloody, and it was decided to implant the left ureter into the dome of the urinary bladder in order to get better drainage without the use of the nephrostomy tube. This operation was performed by Dr. Rolnick on April 21. After this procedure the patient was able to void per urethra and passed up to 58 ounces (1,765 cc.)

Fig. 4 (case 4).—Retrograde pyelogram, showing marked bilateral hydronephrosis and hydroureters.

of urine daily. The nephrostomy tube was then removed. Specimens of urine contained albumin (1 + to 2 +), leukocytes and occasional red blood cells. The blood pressure fell after the operation to 150 systolic and 112 diastolic, but when the patient was discharged, on May 14, it had already returned to the previous high level. The nonprotein nitrogen content of the blood at this time was 76 mg. per hundred cubic centimeters.

Gross Description of the Right Kidney.—The specimen consisted of a kidney weighing 92 Gm. and measuring 9.5 cm. between the poles, 4 cm. in horizontal diameter and 2.5 cm. in thickness (fig. 5). It was covered by densely adherent

fatty tissue, which further surrounded a markedly dilated and thickened ureter, 10 cm. of which was coextensive with the pelvis. The external surface was coarsely nodular. The capsule was stripped with great difficulty or was inseparably

Fig. 5 (case 4).—Surgically removed right kidney, showing thickening and dilatation of the ureter, the renal pelvis and the calices and pyelonephritic scars.

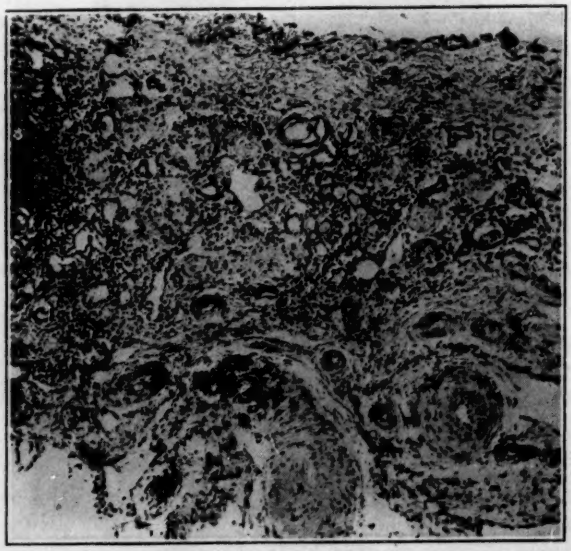

Fig. 6 (case 4).—Pyelonephritic scarred portion of the right kidney. Note the thickened renal capsule, the occasional hyalinized glomeruli, the tubules containing casts, the increase in connective tissue with marked lymphocytic infiltration and the severe arteriosclerosis. (Hematoxylin-eosin stain; × 64.)

adherent to a dark red surface which contained shallow scars and bulbous promontories. On section the cortex and the medulla were indistinguishable. The substance consisted of a gray-red glistening tissue containing hemorrhagic dots. The calices were markedly dilated. The mucosa was glistening, thickened and pale gray-white. The ureteropelvic junction was coextensive, and its dimensions showed little alteration from those of the contiguous parts of the ureter and pelvis. The ureteral mucosa was thickened and striated in many directions.

Histologic Examination of the Right Kidney.—In sections through a depressed scar, the parenchyma was markedly thinned, pelvic mucosa and thickened capsule being visible in a topographic field (fig. 6). Fat tissue was adherent to the thickened capsule, which contained clusters of lymphocytes. The majority of the glomeruli were hyalinized and shrunken. A few swollen glomeruli were very cellular. Fibrous connective tissue outlined the spaces, replaced many tubules and involved the interstitial tissue, which was further extensively infiltrated by lymphocytes, sometimes in follicle formation. The tubules were dilated; they were lined by cuboidal cells and contained colloid-like casts.

The walls of all of the blood vessels were markedly thickened. The small and the medium-sized arteries showed hypertrophy of the muscularis and proliferation of the intima. The lumen of many arterioles was obliterated by swollen endothelial lining cells. The pelvic mucosa was focally squamous in character. The epithelium of many tubules at the tip of the pyramids was of the stratified columnar type. In sections through the promontories interstitial tissue was inconspicuous; the dilated tubules were lined by serrated and vacuolated cells, many of which were desquamated and filled the lumens. The glomerular tufts were large and cellular and generally free within the space. Occasionally proliferated capsule lining cells bound a partially hyalinized glomerulus.

Pathologic Diagnosis.—The pathologic diagnoses were pyelonephritic contracted kidney with hydronephrosis and severe sclerosis of the renal arteries and arterioles.

Comment.—It is most likely that in this case of severe hypertension the bilateral hydroureter and hydronephrosis had existed for a long time before the girl started to complain of headache and visual disturbances. The cause may have been the obstruction at the outlet of the urinary bladder. With prolonged urinary stasis, whatever the cause, there developed a bilateral infection of the urinary tract with pyelonephritis. This is evident in the kidney removed surgically (fig. 5). Secondary to the prolonged pressure atrophy of the hydronephrosis and the pyelonephritic inflammatory process was organic involvement of the arteries and arterioles with considerable narrowing of the lumens, which led to renal "ischemia" and consequent hypertension (fig. 6).

When the patient was first seen in the hospital it was evident that the prognosis was poor because of the extensive, irreparable damage to both kidneys. Fulguration of the obstruction at the neck of the bladder did not help much, because the ureters were already dilated and tortuous. Bilateral nephrostomy was therefore performed, to relieve the intrarenal pressure and to effect better drainage. It was decided to remove the right kidney, since it was observed at operation to be practically functionless and the seat of an inflammatory process. The nephrectomy was not done to lower the blood pressure, since it was understood that the opposite kidney was already damaged, probably

irreversibly. After nephrectomy there was some clinical improvement, and the specific gravity of the urine rose. The final surgical procedure was the implantation of the left ureter into the dome of the urinary bladder to enable the patient to void per urethra without the use of the nephrostomy tube. By this series of operations it is hoped that the impediment to the urinary flow will be overcome.

Sulfanilamide, in doses sufficient to maintain a level between 5 and 10 mg. per hundred cubic centimeters of blood, rendered the urine free of hemolytic streptococci within a week or two, in spite of the marked renal insufficiency. Great care was taken in the administration of the drug because of the impaired ability of the kidneys to excrete it. The drug therapy was repeated with every operative procedure. The intravenous pyelogram, though of some aid in diagnosing the bilateral hydronephrosis, showed the dilated calices only faintly, because of the very poor excretion of the dye. However, a retrograde pyelographic examination (fig. 4) definitely demonstrated the hydronephrosis and the hydroureters, and the procedure was carried out without any ill effects to the patient. It is remarkable that in spite of the marked hypertension and the severe renal disease this child was able to undergo so many surgical procedures with relatively rapid convalescence after each.

The prognosis, of course is poor because of the damage to the remaining kidney. Although the patient was ambulatory and able to carry on many of her usual activities for several months, she is now again confined to bed in the hospital. Her hypertrophied and dilated heart has failed again, and signs of congestive heart failure, such as orthopnea, dependent edema and enlargement and tenderness of the liver, are present. The hypertension has persisted; the systolic pressure is well above 200 and the diastolic over 120. When she is given as much water as she desires, she still excretes large quantities of urine of low specific gravity.

CASE 5.—*Traumatic rupture of a hydronephrotic kidney.*[22]

J. D. L., a 7 year old white girl, fell over a chair and experienced sharp pain in her left side. This was followed by severe weakness and vomiting. She was admitted to Sarah Morris Hospital for Children four hours later (on Sept. 25, 1940).

Physical examination on admission revealed a well developed girl who did not appear ill and who apparently was not in acute distress. The temperature was 98 F., and the pulse rate was 88 and the respiratory rate 22 per minute. The blood pressure was 134 systolic and 90 diastolic. The only abnormality was in the abdomen, which showed tenderness and voluntary rigidity in the left upper quadrant. No mass was palpable, however. There was no abdominal distention. The red cells numbered 4,500,000 and the white cells 22,150 per cubic millimeter, and the hemoglobin content was 80 per cent. Catheterization produced 8 ounces

22. Permission to report this case was granted by Dr. J. S. Grove.

(237 cc.) of bloody urine. In her past history there was little of significance, except that she had been in Sarah Morris Hospital for Children at the age of 7 months, with bronchopneumonia. Specimens of urine examined during that hospitalization were normal.

On the day after admission her general condition remained good. Blood pressure readings varied between 130 and 134 systolic and 88 and 94 diastolic. The urine was still grossly bloody but contained less blood than the catheterized specimen obtained on admission. Tenderness and rigidity were still present over

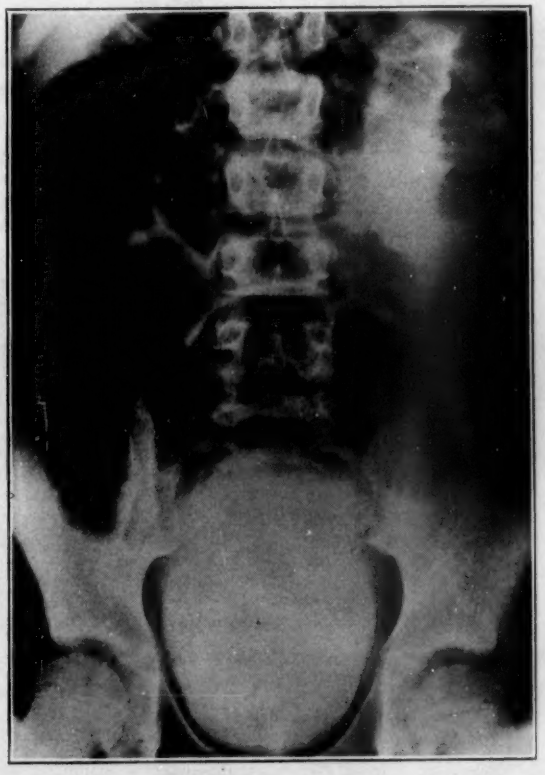

Fig. 7 (case 5).—Intravenous pyelogram (taken forty-five minutes after injection of the dye), showing presence of the opaque material extraneous to the left kidney, probably within the renal capsule.

the left upper quadrant of the abdomen. The report on an intravenous urogram was as follows:

"Opaque material appears in both renal outlines after five minutes. On the right the dye material outlines a renal pelvis which appears somewhat dilated, but the fornices of the calix are well cupped throughout. The right ureter is of normal caliber and pursues an anatomic course to the bladder. Excretion of the opaque material on the left gives rise to a rather grotesque appearance. The renal outline per se cannot be made out, nor is the renal pelvis visualized. There appears to be dye material present in what would correspond to a form of dilated hydro-

nephrotic or pyonephrotic calices. Examination after forty-five minutes (fig. 7) further reveals the presence of opaque substance extraneous to the kidney, probably within the renal capsule. Minimal absorption and excretion of this dye material have occurred. The left ureter is not visualized at any time. The bladder is normal in size and contour. The impression is of old, left hydropyonephrosis on which is superimposed a traumatic rupture."

On September 27 a definitely palpable, tender mass was present under the left costal margin anteriorly, and it was assumed that the hemorrhage was increasing. The blood pressure remained at 130 systolic and 90 diastolic. Surgical intervention was deemed advisable, and when the left anterior perirenal capsule was opened a large amount of bloody urine welled up into the incision. A large tear was found in the renal pelvis, and nephrectomy was performed by Dr. J. S. Grove. The postoperative convalescence was uneventful. The urine became free

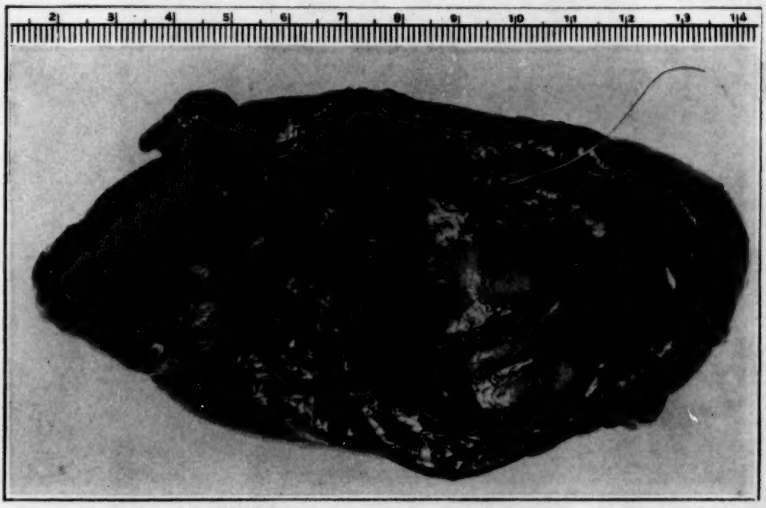

Fig. 8 (case 5).—Surgically removed left kidney, showing hydronephrosis and large tear in the renal pelvis.

of red blood cells. The blood pressure on the first postoperative day was 115 systolic and 80 diastolic; during the next two weeks it varied between 98 and 100 systolic and 65 and 70 diastolic (with the patient resting in bed). Three months later, when the patient visited the clinic, the blood pressure was 110 systolic and 80 diastolic, and after another three months, when the patient was ambulatory, 110 systolic and 60 diastolic.

Gross Examination of the Left Kidney.—The specimen consisted of a kidney weighing 111 Gm. and measuring 12.9 by 4.2 cm. in its greatest dimensions (fig. 8). It was cystic in consistency, and the pelvis was markedly dilated. There was an irregular opening in its most proximal portion, measuring 6.4 by 4.2 cm. The mucosa in the region of this defect was hemorrhagically discolored. The capsule was thin and stripped readily, revealing a surface which in general was pale, tan-gray, smooth and glistening. In several areas along the convex border there were depressed scars with grayish bases. The renal calices were markedly dilated and the medulla markedly atrophic, the pyramids being completely indistinguishable.

The cortex in several places was very thin, measuring as little as 4 mm. in thickness.

Histologic Examination of the Left Kidney.—Sections revealed the presence of the cortex only, there being no evidence of the medulla. The glomeruli, the arteries and the arterioles showed no histologic changes. The tubules showed varying degrees of cloudy swelling and occasionally contained desquamated lining cells. There were a few subcapsular areas of lymphocytic infiltration corresponding to the depressed scars noted in the gross specimen.

Comment.—Although the hypertension in this case was not marked, both the systolic pressure and, probably more significantly, the diastolic pressure were above normal, as was indicated by the fall in blood pressure following nephrectomy. One would have expected a lowered blood pressure to follow the visceral damage and hemorrhage. The hypertension may have been a consequence of either (1) the hydronephrosis (fig. 8) or (2) the subcapsular extravasation of urine and blood (fig. 7). On the other hand, the elevated blood pressure may have been due to a combination of these two factors.

There has been a gradual accumulation of experimental and clinical evidence showing that hydronephrosis can cause hypertension in both the acute and the chronic stage. In 1910 Rautenberg [23] occluded one ureter in a series of 6 rabbits over a period of two or three weeks. After this he extirpated the contralateral kidney. In 5 of the rabbits definite hypertension developed in about nine months. The kidney in each case showed marked hydronephrosis without inflammatory or vascular changes. Hartwich [24]; Levy, Mason, Harrison and Blalock,[25] and Megibow, Friedberg, Rodbard and Katz [26] have demonstrated in dogs that a transient rise in blood pressure occurs after unilateral or bilateral ureteral occlusion. Williams, Wegria and Harrison [27] found that rats with spontaneous bilateral hydronephrosis showed definite elevation of the blood pressure, while those with spontaneous unilateral hydronephrosis sometimes did. Ligation of one ureter for several days caused slight hydronephrosis but no constant rise in blood pressure.

23. Rautenberg, E.: Erzeugung chronischer Nierenerkrankungen mit folgender Blutdrucksteigerung und Arteriosclerose, Deutsche med. Wchnschr. **36**:550, 1910.

24. Hartwich, A.: Der Blutdruck bei experimenteller Urämie und partieller Nierenausscheidung, Ztschr. f. d. ges. exper. Med. **69**:462, 1930.

25. Levy, S. E.; Mason, M. F.; Harrison, T. R., and Blalock, A.: The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs, Surgery **1**:238, 1937.

26. Megibow, R. S.; Friedberg, L.; Rodbard, S., and Katz, L. N.: Changes in Arterial Pressure After Bilateral Complete or Partial Ureteral Occlusion, Proc. Soc. Exper. Biol. & Med. **43**:245, 1940.

27. Williams, J. R., Jr.; Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, Arch. Int. Med. **62**: 805 (Nov.) 1938.

Beckwith [28] showed that after unilateral ureteral ligation in rats the greatest average blood pressure response was elicited by injection of extracts of those hydronephrotic kidneys removed twenty-four to forty-eight hours after ureteral ligation.

Therefore it is evident that both acute and chronic experimental hydronephrosis may cause arterial hypertension. The factors involved appear to be (1) renal "ischemia" due to the decreased renal blood flow as a consequence of the increased intratubular pressure and pressure on the renal vascular tree and (2) decrease in the amount of normal metabolizing renal tissue (Rodbard and Katz [29]).

In the literature there is an increasing number of reports of clinical cases to support the contention that hydronephrosis either unilateral or bilateral may be the cause of arterial hypertension. Furthermore, it has become evident that removing the unilateral hydronephrotic kidney in some cases will result in the fall of the blood pressure to normal levels. Bartels and Leadbetter [30] reported the case of a 37 year old woman whose blood pressure varied between 200 and 170 systolic and 120 and 80 diastolic. After removal of the hydronephrotic kidney, the arterioles of which showed slight thickening, the blood pressure declined to normal and remained there for the ten months she had been followed up postoperatively. Nesbit and Ratliff [31] mentioned the case of a 20 year old man who had had hypertension (systolic pressure 180 and diastolic 90) for at least three years. After removal of the left kidney, which was nothing more than a hydronephrotic sac, the blood pressure returned to normal. The same authors [32] also reported the case (case 13) of a 41 year old man whose retrograde pyelograms revealed marked bilateral hydronephrosis. The blood pressure was 190 systolic and 100 diastolic. Bilateral nephrostomy was performed in two stages; after the first stage the blood pressure still remained at the same hypertensive level, but after the second stage it fell to normal and remained there.

In our case the subcapsular extravasation of urine and blood may have played a role in the causation of the hypertension. In children

28. Beckwith, J. R.: The Effect of the Time Factor on the Amount of Pressor Material Present in Kidney After Unilateral Ligation of Renal Pedicle and After Unilateral Ligation of Ureter, Am. J. Physiol. **132**:1, 1941.

29. Rodbard, S., and Katz, L. N.: The Elimination of the Effect of the Chemical Mediator of Renal Hypertension, Am. J. M. Sc. **198**:602, 1939.

30. Bartels, E. C., and Leadbetter, W. F.: Hypertension Associated with Unilateral Non-Infected Hydronephrosis Treated by Nephrectomy, Lahey Clin. Bull. **1**:17, 1940.

31. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Renal Disease, J. A. M. A. **116**:194 (Jan. 18) 1941.

32. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Nephropathy, J. Urol. **43**:427, 1940.

injuries to abdominal organs (including the kidney) are likely to be associated with shock, evidenced by pallor, rapid small pulse, vomiting and weakness (Beer and Hyman [33]), which, of course should cause a drop in blood pressure. Recently it has become evident that instead there may actually be an elevation of the blood pressure after an injury to the kidney. Sobel [1] reported the case of a 4 year old boy who fell down stairs, experienced pain in the left flank and passed almost pure blood in the urine. Renal function was normal, but determination of the blood pressure, done for the first time three weeks after the accident, revealed marked hypertension (systolic pressure 170 and diastolic 120). This persisted, though in definitely lessening degree, for the remaining five weeks of his stay in the hospital; at discharge the blood pressure was 128 systolic and 80 diastolic. One year later it was 116 systolic and 70 diastolic. The author attributed the hypertension to the perirenal hematoma resulting from the fall which caused renal ischemia by the same mechanism that operates in perinephritis caused by renal constriction with cellophane (Page [34]). With absorption of the hematoma the blood pressure returned to normal. Engel [35] reported the somewhat similar case of a 26 year old man who was admitted to the hospital with the typical signs of an intracapsular rupture of the kidney associated with rather profuse hematuria over a period of eleven days. Conservative management was adopted, and no operation was performed. However during his hospitalization the blood pressure mounted to as high as 160 systolic and 100 diastolic and then gradually subsided as the bleeding ceased and he improved.

Our case substantiates the opinion of urologists that hydronephrotic kidneys, especially in children, are more susceptible to damage from slight trauma (such as the falling over a chair which occurred in our case) than normal kidneys. Moreover, our case may add support to the contention that hydronephrotic kidneys can be the cause of a hypertension which may be dissipated by the removal of that kidney. However, the possibility that the subcapsular extravasation of blood and urine was the mechanism by which the hypertension was produced must be considered. Since there were no determinations of blood pressure before the injury was sustained, no final decision can be reached as to the roles of the hydronephrosis and the subcapsular extravasation of fluid in initiating the hypertension.

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33. Beer, E., and Hyman, A.: Diseases of the Urinary Tract in Children, New York, Paul B. Hoeber, Inc., 1930, pp. 212, 215 and 216.

34. Page, I. H.: The Production of Persistent Arterial Hypertension by Cellophane Perinephritis, J. A. M. A. **113**:2046 (Dec. 2) 1939.

35. Engel, W. J.: The Association of Unilateral Kidney Disease with Hypertension, Cleveland Clin. Quart. **7**:290, 1940.

CASE 6.—*Subacute glomerulonephritis with arteriolonecrosis.*

E. B., a 14 year old white girl, was admitted to Sarah Morris Hospital for Children on Sept. 4, 1930 with a history of hematuria and swelling of the ankles of four months' duration and puffiness of the eyelids and the face for a somewhat shorter period. She had had diphtheria at the age of 4 years and frequent sore throats until five years before admission, when her tonsils were removed.

Physical Examination.—Examination revealed a well developed girl showing slight edema of the eyelids and marked edema of the lower extremities. The thyroid was enlarged bilaterally. The heart was enlarged to the left, and a systolic murmur was heard over the entire precordium, loudest over the pulmonic area. The aortic second sound was accentuated. The temperature and the pulse and respiratory rates were within normal limits. The arterial blood pressure was 140 systolic and 80 diastolic.

Laboratory Data.—The Wassermann and Kahn reactions of the blood were negative. The red cells numbered 3,640,000 and the white cells 11,500 per cubic millimeter of blood; the hemoglobin content was 65 per cent. Examination of the blood showed nonprotein nitrogen, 32 mg. per hundred cubic centimeters; urea nitrogen, 15 mg.; uric acid, 4.4 mg.; creatinine, 1.6 mg.; chlorides, 617 mg.; calcium, 9 mg.; inorganic phosphorous, 6.7 mg.; cholesterol, 250 mg., and total plasma proteins, 5.7 Gm., of which 2.3 Gm. was albumin and 3.4 Gm. globulin. Examination of the urine showed a specific gravity of 1.020, albumin (2+) and many leukocytes, red blood cells and casts. The values for the basal metabolic rate ranged from —7.6 to —31.9 per cent.

Course.—During the first month in the hospital the blood pressure gradually increased and on October 11 was 152 systolic and 96 diastolic. The level of nonprotein nitrogen was 47 mg. and that of creatinine 2 mg. per hundred cubic centimeters of blood. Examination of the urine gave results similar to those obtained at admission. Moderate peripheral edema was present, but the patient felt well. There was no further change in her course until November 2, when she became more edematous, ascites appeared and she began to complain for the first time of visual disturbances. Examination of the ocular fundi on that day revealed no abnormalities. The blood pressure now was 205 systolic and 132 diastolic. Unfortunately, no blood pressure determinations had been recorded during the previous three weeks; so it was impossible to say whether the blood pressure had risen gradually since the last determination or whether it had suddenly become markedly elevated. The nonprotein nitrogen of the blood measured 44 mg. per hundred cubic centimeters and the creatinine 2.1 mg. On the next day visual disturbances became more severe, and the patient began to have clonic convulsions followed by semicoma and transient periods of pulmonary edema. Examination of the eyegrounds now showed choked disks but no retinitis. Intravenous administrations of dextrose and magnesium sulfate, venesection and spinal puncture afforded slight relief. The urine showed no changes until three days later, when examination showed albumin (4+), innumerable leukocytes, red blood cells and cellular casts. After this the patient had frequent episodes of severe headache, nausea, vomiting and convulsions. The blood pressure varied between 170 systolic and 112 diastolic and 236 systolic and 175 diastolic. Examination of the eyegrounds on December 15 revealed narrowing of the retinal arteries and dilated and tortuous veins. The nerve heads were hemorrhagic in spots. There were bilateral choked disks, about which there were hemorrhages and exudates. Examination of the blood showed that the level of nonprotein nitrogen had increased to 64 mg. per hundred cubic centimeters and that of creatinine to

3 mg. and that the total plasma protein content had decreased to 4.94 Gm. The urine continued to show numerous leukocytes, red blood cells and casts. The patient died on February 7, of pulmonary edema.

Clinical Diagnosis.—The clinical diagnoses were (1) chronic glomerulonephritis with marked tubular changes; (2) generalized anasarca, with edema of the lungs, bilateral hydrothorax, pericardial effusion, ascites and subcutaneous edema, and (3) cardiac hypertrophy.

Necropsy.—Gross Examination: The kidneys together weighed 325 Gm. The capsules stripped with ease, revealing finely granular surfaces on which pinpoint hemorrhages were clearly visible. There were also smaller, light grayish yellow areas scattered over the surfaces. The organs cut with slightly increased resistance, and the cut surfaces showed an indistinct cortical architecture with many

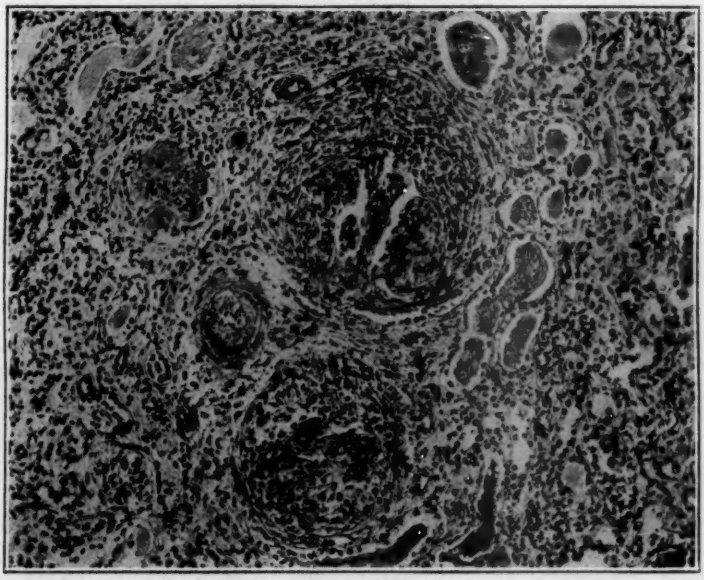

Fig. 9 (case 6).—Subacute (extracapillary) glomerulonephritis with marked crescent formation and arteriolonecrosis. (Hematoxylin-eosin stain; × 84.)

hemorrhagic dots. At the corticomedullary junction there were fine golden yellow striations which extended up into the cortex. The pelves and the ureters showed no changes. In the urinary bladder there was a small blood clot; however, the bladder itself was normal grossly.

The heart was hypertrophied; it weighed 350 Gm. The left ventricle measured 2.1 cm. in thickness, and the right ventricular wall was 0.2 cm. thick. Otherwise, the heart showed no abnormalities. The lungs were edematous, and in the lower lobe of the left lung there were several elevated, friable, reddish gray areas.

Throughout the mucosa of the large intestine there were small, discrete and confluent areas of hemorrhage, some of which were slightly ulcerated. Elsewhere the bowel wall was edematous.

Also observed were generalized edema of the subcutaneous tissue, ascites, bilateral hydrothorax and pericardial effusion.

Histologic Examination: Kidneys: The sections were characterized by diffuse involvement of the glomeruli (fig. 9). Most of them were enlarged and showed marked swelling and proliferation of the epithelial and endothelial cells. There was also marked proliferation of the capsular epithelium with the formation of epithelial crescents, some of which were adherent to the glomerular tufts. The glomerular loops sometimes showed atrophic changes, and occasionally completely hyalinized glomeruli were observed. The capsular spaces often contained red blood cells, leukocytes and coagulated exudate. Some of the glomeruli were partially or completely necrotic, and frequently the vasa afferentia of such glomeruli showed arteriolonecrosis. The walls of such vessels were smudgy and without definite outlines; occasionally red blood cells or polymorphonuclear leukocytes were seen within or just without the vessel walls. The intralobular arteries often showed subendothelial proliferation of cells, with narrowing of the lumen. The lining cells of the convoluted tubules were swollen, granular and vacuolated. Sudan stain revealed the presence of many fat globules in these cells. The lumen of the tubules frequently contained desquamated epithelial cells, red blood cells, leukocytes and casts. The interstial tissue was moderately increased and was infiltrated with lymphocytes. The renal pelvis showed no inflammatory changes.

Large Intestine: Sections from the large intestine showed areas of recent hemorrhage in the mucosa and submucosa. The latter was edematous, and in focal areas, usually in the vicinity of the hemorrhages, there were accumulations of lymphocytes, endothelial leukocytes and polymorphonuclear leukocytes. Frequently these cells were seen in perivascular locations. The arterioles often showed marked swelling and proliferation of the endothelial cells.

Pathologic Diagnosis.—The pathologic diagnoses were subacute (extracapillary) glomerulonephritis with superimposed acute hemorrhagic glomerulonephritis and arteriolonecrosis; lipoid degeneration of the kidney (lipoid nephrosis); hypertrophy of the heart, especially of the left ventricle; anasarca; bilateral hydrothorax; hydropericardium; ascites; pulmonary edema; bronchopneumonia, of the lower lobe of the left lung, and acute hemorrhagic and ulcerative colitis.

Comment.—Although in many respects this case is typical of subacute glomerulonephritis with the nephrotic component, it is particularly interesting because opportunity was afforded of following the development of the marked hypertension during the patient's hospital course. The patient apparently had acute glomerulonephritis four months before admission to the hospital. On admission her blood pressure was 140 systolic and 80 diastolic, and the nonprotein nitrogen content of her blood was 32 mg. per hundred cubic centimeters. Two months later, at the time that she had a severe attack of visual disturbances, convulsions and a marked increase in the number of leukocytes, red blood cells and casts in the urine, her blood pressure was 205 systolic and 132 diastolic. The nonprotein nitrogen content of the blood at that time was 44 mg. per hundred cubic centimeters. Examination of the eyegrounds revealed choked disks without retinitis, but five weeks later hemorrhages and exudates were also present. The marked hypertension persisted until death, which occurred five months after admission. Before death the nonprotein nitrogen content of the blood rose to 64 mg. per hundred cubic centimeters.

It is possible that the malignant phase of the hypertension commenced at the time when the convulsions, increase in cellular elements and casts in the urine and onset of marked hypertension occurred. Both kidneys showed severe subacute glomerulonephritis with marked arteriolonecrosis (fig. 9) but the arteriolonecrosis must have occurred late in the course of the disease, in view of the microscopic appearance of the vessels.

Löhlein [36] pointed out that necrotizing changes in the renal arterioles had occurred in from 10 to 20 per cent of the cases of late acute and early subacute glomerulonephritis he observed in which autopsy was performed. Such changes occurred in the cases characterized by what Löhlein called a "stormy course," in which there is the characteristic histologic picture of extracapillary glomerulonephritis. Jaffé [37] examined histologic material in 94 cases of acute and subacute glomerulonephritis in 5 of which the sections showed marked alterations of the arterioles. They were necrotic and surrounded by leukocytes and lymphocytes, which invaded the structureless wall and filled the lumen. He believed that such arteriolitis could not be due to mechanical injury but must result from toxic irritation. Fishberg [38] observed acute necrotizing arteritis in the renal arterioles in 3 of 8 cases of diffuse glomerulonephritis in which the patient died during the acute stage of the disease. One of the cases reported was that of a 33 year old man who had severe acute diffuse glomerulonephritis (without edema) and died in one month of pronounced renal insufficiency (in uremia). His blood pressure was 104 systolic and 68 diastolic. Fishberg expressed the belief that this case was of particular significance because since there was no arterial hypertension the acute arteriolar lesions could not have been due to the mechanical factor of arterial hypertension and must be considered as toxic in origin. He stated, as had Löhlein, that arteriolar lesions probably should be attributed to the same agent that produced the glomerulonephritis, the arteriolar lesions being part of the glomerulonephritis.

In our case two factors may have combined to produce the arteriolonecrosis, (1) the marked arterial hypertension and (2) renal insufficiency. It is evident, however, that the hypertension preceded the renal insufficiency, which even shortly before death was not marked.

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36. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570, 1917.

37. Jaffé, R. H.: The Vascular Changes of the Kidney in Hypertension, Am. J. M. Sc. **169**:88, 1925.

38. Fishberg, A. M.: The Arteriolar Lesion of Glomerulonephritis, Arch. Int. Med. **40**:80 (July) 1927.

SUMMARY AND CONCLUSIONS

The case histories of children with persistent arterial hypertension admitted to the Sarah Morris Hospital for Children of Michael Reese Hospital during the past eleven years have been studied. Only those in which one or both kidneys were available for pathologic investigation have been selected for detailed analyses, and only 1 of the 3 cases of hypertension due to subacute or chronic glomerulonephritis has been included. Although chronic glomerulonephritis is usually accompanied by hypertension, it is a relatively less frequent cause of hypertension in children than was heretofore assumed.

Six cases of renal hypertension are reported in detail, with clinical and pathologic observations. In 4 the kidneys were obtained for study at autopsy, and in 2 a kidney was removed at operation. The diagnoses in the cases were as follows: (*a*) congenital unilateral hypoplasia of the kidney with nephrosclerosis, (*b*) chronic bilateral pyelonephritis with contraction of the kidneys, (*c*) chronic bilateral pyelonephritis with arteriolonecrosis, (*d*) bilateral hydronephrosis with chronic pyelonephritis, (*e*) traumatic rupture of a hydronephrotic kidney and (*f*) subacute glomerulonephritis with arteriolonecrosis.

An attempt is made to explain the hypertension on the basis of the pathologic observations in the light of the newer concepts about the physiologic aspects of hypertension. The interference with the renal vascular supply which was shown anatomically could have been responsible for the hypertension in each case.

In the majority of these cases the disease might have responded to urologic management if the hypertension had been detected in its early stages before irreversible damage had occurred, or if the renal condition had been diagnosed even before the hypertension became manifest.

In the majority of the cases of persistent hypertension in children in which the kidneys have been examined pathologically the disease was of renal origin.

Dr. Louis N. Katz, head of the cardiovascular department, and Dr. Otto Saphir, head of the department of pathology, gave suggestions and criticisms.

News and Comment

SOCIETY NEWS

Southern Medical Association.—Dr. Harvey F. Garrison, of Jackson, Miss., a well known pediatrician of Mississippi, has been elected president of the Southern Medical Association.

PERSONAL NEWS

Dr. Horton R. Casparis Elected.—Dr. Horton R. Casparis, of Nashville, Tenn., has been elected president of the American Board of Pediatrics, to replace Dr. Borden S. Veeder, of St. Louis, whose term expires.

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

THE BACTERIOSTATIC ACTION OF SULFANILAMIDE UPON HEMOLYTIC AND NON-HEMOLYTIC ENTEROCOCCI. ERWIN NETER, J. Bact. **40**:383 (Sept.) 1940.

There is practically no doubt that sulfanilamide and allied compounds have a definite effect both in vitro and in vivo on a large variety of quite unrelated micro-organisms. However, studies have not been very conclusive concerning the action of sulfanilamide on hemolytic and nonhemolytic enterococci. The author thought, therefore, that it would be worth while to make an investigation on the enterococcus group. A rather exhaustive study was carried out, the details of which should be obtained by examining the original paper. It was observed that sulfanilamide (concentration of 1 per cent) may be bacteriostatic toward suitable numbers of both hemolytic and nonhemolytic enterococci in a maltose broth medium containing 6.5 per cent sodium chloride, for there was a rapid decrease in the number of viable enterococci, while a marked increase took place in the control broth. If the culture contained too many organisms little change was noted. The temperature of the medium played an important part. At 43 C. sulfanilamide in a concentration of 1 per cent was markedly more bacteriostatic toward hemolytic enterococci than at 37 C. The sulfanilamide broth incubated at 43 C. may become rapidly sterile at a time when the control broth incubated at 43 C. and a sulfanilamide broth incubated at 37 C. contain large numbers of viable micro-organisms. The author feels that his investigations are thorough enough to warrant the conclusion that these in vitro experiments definitely indicate that sulfanilamide in a concentration of 1 per cent is bacteriostatic toward both hemolytic and nonhemolytic enterococci. The drug may also enhance the rate of decrease in the number of viable enterococci in vitro.

STOESSER, Minneapolis.

THE ACTIVITY OF CHEMOTHERAPEUTIC AGENTS. RAYMOND L. LIBBY, J. Bact. **40**:733 (Nov.) 1940.

Various authors have pointed out that there appears to be a quantitative relation between the effective bacteriostatic concentration of a chemotherapeutic agent and the number of bacteria. The author feels, however, that most of the methods used in studying the in vitro action of the drugs do not lend themselves to a precise evaluation of the results, because of their inherent errors. He therefore developed a simple and rapid method for demonstrating the in vitro activity of chemotherapeutic agents on susceptible micro-organisms. It involves a comparison of the population densities in drug-containing and control tubes during a four hour incubation period. The population densities were determined by means of photronreflectometric turbidity readings. Interesting results were obtained. There was a rapid multiplication of the organisms in both the control and the drug-containing tubes. The difference in population numbers between the drug-containing and the control tubes was small at the end of two hours but became progressively greater with increased incubation time up to four hours. No indication of a lag phase prior to the apparent action of the drugs on susceptible organisms was observed.

The author states: "The effect of the drugs on susceptible organisms was directly related to the concentration of the drug, within certain limits prescribed by the degree of activity of the drugs and the susceptibility of the organisms used in the test.

"The effect of the drugs on susceptible organisms was indirectly related to the size of the initial inoculum.

"There appears to be a more rapid increase in the total population as indicated by photronreflectometric turbidity readings than in the number of viable organisms as indicated by plate counts when susceptible organisms are grown in the presence of highly active drugs."

These observations may indicate that the action of sulfanilamide and its derivatives is bactericidal and that this effect is produced immediately on a small percentage of susceptible organisms.

STOESSER, Minneapolis.

RAPID DIAGNOSTIC METHOD FOR TESTING THE VIRULENCE OF CORYNEBACTERIA. VERA B. DOLGOPOL and HELEN Y. MARKUS, J. Lab. & Clin. Med. **26**:553 (Dec.) 1940.

The authors describe a four day method for the determination of the virulence of the organisms of the Corynebacterium group. Tests carried out with pure cultures require at least five or six days.

GARD, Galveston, Texas.

Metabolism; Infant Feeding; Milk and Other Foods

SOME CONCLUSIONS FROM OBSERVATIONS ON OBESE CHILDREN. JULIUS BAUER, Arch. Pediat. **57**:631 (Oct.) 1940.

The frequent combination of overweight and overgrowth in children cannot always be explained by an excessive intake of food. Children may be obese as a result of an individual constitutional factor, the combination of abnormal genes for both obesity and overgrowth (gigantism).

The time at which the effects of such abnormal genes appear may vary considerably. Their manifestation may even take place in fetal life in which case, according to Christiansen, the subject may be said to have macrosomia adiposa congenita. In all other varieties, in which there is a later manifestation of effects, the pathologic condition is essentially the same as far as nature, cause and pathogenesis are concerned, the difference being merely that such types of macrosomia adiposa are not congenital.

ORR, Buffalo.

IODINE IN DRINKING WATERS, VEGETABLES, COTTONSEED MEAL, AND ROUGHAGES. G. S. FRAPS and J. F. FUDGE, Bulletin 595, Texas Agricultural Experiment Station, November 1940.

This bulletin presents the results of a study of the iodine content of vegetables, cottonseed meal and roughages produced in Texas and of the iodine and salt contents of 103 samples of city water and 12 samples of rural water.

The iodine content of the samples of city water varied from 4 to 312 parts per billion, that of 37 samples of vegetables from 112 to 3,502, that of 235 samples of cottonseed meal from 32 to 1,420, that of 6 samples of coarse roughage from 53 to 835, that of 5 samples of hay from 90 to 550 and that of 42 samples of grass from 17 to 1,086.

The iodine content of Texas city water, well water, vegetables, cottonseed meal, roughages and grasses is sufficiently high to insure an adequate intake of iodine by man and animals under ordinary conditions. In most cases, much more iodine is present than is required. The amount of iodine in Texas foods, feeds and water is much higher than that in similar material from areas where goiter is common.

The use of iodized table salt in Texas, except under the supervision of a competent physician, and the use of iodized mineral mixtures for livestock are not recommended.

FROM THE AUTHORS' SUMMARY.

A Comparison of the Nutritive Values of Raw, Pasteurized and Evaporated Milks for the Dog. H. D. Anderson, C. A. Elvehjem and J. E. Gonce Jr., J. Nutrition **20**:433 (Nov.) 1940.

These Wisconsin investigators found that the use of a diet of whole raw milk supplemented with iron, copper, manganese and cod liver oil allowed normal growth and reproduction in dogs. However, when evaporated or pasteurized milk was fed under similar conditions, most of the pups born showed either muscular dystrophy or a hemorrhagic condition of the brain, the lungs and the pericardium. However, the symptoms were less pronounced in those dogs given the fortified pasteurized milk. The administration of vitamin E was effective in preventing and curing the muscular dystrophy. A suggestion was made that the intake of vitamin K may be related to the hemorrhagic condition, and a further investigation is now being carried out.

Only repeated pregnancy and lactation produced these deficiencies, since "all the milks supported good growth of the males for almost 3 years and maintained the females in good condition except under the added strain of reproduction."

Fredeen, Kansas City, Mo.

The Influence of Lactose on Calcium Retention in Children. Rosalind Mills, Herta Brieter, Elizabeth Kempster, Beula McKey, Marjorie Pickens and Julia Outhouse, J. Nutrition **20**:467 (Nov.) 1940.

In their study of the calcium balances of 5 boys, between the ages of 5 and 7 years, the authors found an average increase of 33.5 per cent in calcium retention when the diet was supplemented with 36 Gm. of lactose daily over a period of six to nine consecutive weeks.

Fredeen, Kansas City, Mo.

Dried Milk Fevers. Raimundo Martagão Gesteira, Bol. Inst. de puericult. **2**:25, 1940.

The author has written a general review of fevers caused by the use of dried milk in Brazil. After giving a historical outline of the subject, he describes the symptomatology and comments on the various theories of pathogenesis. He points out that high concentrations of dried milk have been fed in described cases, and he concludes that the pyrexia in such cases is a "concentration fever," due simply to dehydration. He divides dried milk fever into three types: (1) concentration fevers, (2) fevers caused by chemical alterations of the dried milk (digestive disorders produced by the milk itself) and (3) anaphylactic fevers caused by a reaction to the milk proteins.

The author does not consider as examples of true dried milk fever those cases in which anaphylaxis or reaction to chemical alterations of the milk itself cannot be proved. Finally, in the presence of fevers of unascertainable cause he recommends examination or change in the milk being fed, since such a procedure may save the physician's time and relieve the patient.

Soto, Habana, Cuba.

Vitamins; Avitaminoses

Parenteral Administration of a Water-Soluble Compound with Vitamin K Activity: 4-Amino-2-Methyl-1-Naphthol Hydrochloride. Edward R. Anderson, John E. Karabin, Herbert Udesky and Lindon Seed, Arch. Surg. **41**:1244 (Nov.) 1940.

The oil-soluble vitamin K (2-methyl-1, 4-naphthoquinone) has been found inconvenient for parenteral use, so a water-soluble compound with vitamin K activity, 4-amino-2-methyl-1-naphthol hydrochloride, has been synthesized by Doisy and his associates. This preparation, which the authors designate as vitamin K_5, can be given by the parenteral route. It was used effectively for 17 of 18 patients with hypoprothrombinemia. It was found that intravenous administration

is superior to intramuscular. The intravenous dose is approximately 2 to 3 mg. daily. The response occurs within three quarters of an hour to one and one-half hours after administration. Bile salts are not necessary for the action of the drug when it is given either intravenously or intramuscularly. The effect of vitamin K_5 is no greater than that noted after the use of the water-insoluble vitamin K compound, but vitamin K_5 has the distinct advantage that it can be given at any time in the preoperative or postoperative course, regardless of whether the patient is able to take and absorb drugs by mouth.

KAISER, Rochester, N. Y.

DETERMINING RIBOFLAVIN IN DRIED MILK PRODUCTS: II. SEASONAL VARIATIONS. ROYAL A. SULLIVAN and EVELYN BLOOM, J. Milk Technol. **3**:346 (Dec.) 1940.

Dried milk products are the most important source of riboflavin for animal and poultry feeding. Therefore it was important to determine the seasonal variations in the riboflavin content of whey from cheese, since it contains the major portion of the riboflavin content of whole milk.

Samples were obtained bimonthly from six drying plants in five different states. The average concentration was 25.1 micrograms of riboflavin per gram of whey. A statistically significant difference between the mean value for winter and that for other seasons was found. This maximum deviation amounted to only 7 per cent of the total concentration of riboflavin, which was considered insignificant for practical feeding purposes. This seasonal variation was not a simple phenomenon due to a reduction in the intake of riboflavin but was dependent on several factors, such as increased secretion of milk which resulted in a negative correlation between riboflavin concentration and milk production.

FLOOD, San Francisco.

RELATION OF PANTOTHENIC ACID TO THE FILTRATE FRACTION OF THE VITAMIN B COMPLEX. MILDRED K. DIMICK and ALBERT LEPP, J. Nutrition **20**:413 (Nov.) 1940.

On the basis of their experimental work with chicks and rats Dimick and Lepp conclude that pantothenic acid is an important part of the "filtrate factor" but by no means represents the whole "factor." They add that a rice bran concentrate contains a factor (or factors) which promotes growth in chicks and rats in addition to the other components of the vitamin B complex, namely, thiamine, riboflavin, pyridoxine, nicotinic acid and pantothenic acid.

FREDEEN, Kansas City, Mo.

THE DISTRIBUTION OF THE "GRASS JUICE FACTOR" IN PLANT AND ANIMAL MATERIAL. S. B. RANDLE, H. A. SOBER and G. O. KOHLER, J. Nutrition **20**:459 (Nov.) 1940.

The authors present a table showing the distribution of the "grass juice factor" in plant and animal tissues. Young plant tissues are much richer in this growth-promoting substance than those of the older, more mature plant. Animal tissue apparently is a poor source of this factor.

FREDEEN, Kansas City, Mo.

THE EFFECT OF PYRAZINE ACIDS AND QUINOLINIC ACID ON THE V-FACTOR CONTENT OF HUMAN BLOOD AND UPON CANINE BLACKTONGUE. W. J. DANN, H. I. KOHN and P. HANDLER, J. Nutrition **20**:477 (Nov.) 1940.

The authors concluded that oral administration of quinolinic acid, pyrazine monocarboxylic acid or pyrazine 2, 3-dicarboxylic acid did not affect the content of the the V factor (coenzymes I and II and possibly unknown related compounds) of human blood. Also, these three acids were not as effective as nicotinic acid in the treatment of canine blacktongue.

FREDEEN, Kansas City, Mo.

PLACENTAL AND MAMMARY TRANSFER OF VITAMIN E IN THE RAT. K. E. MASON and W. L. BRYAN, J. Nutrition **20**:501 (Nov.) 1940.

The placental transmission of vitamin E in the rat is extremely limited; the vitamin is much more readily transferred through the mammary gland to the milk.

FREDEEN, Kansas City, Mo.

A RAPID METHOD OF DIFFERENTIATING CHILDREN WITH LARGE OR SMALL RESERVES OF VITAMIN C. JOHN PEMBERTON, Brit. M. J. **2**:217 (Aug. 17) 1940.

Tests were made to determine the amount of ascorbic acid in the urine after a test dose of ascorbic acid had been administered to subjects whose diet contained moderate amounts of fresh fruits and vegetables. The urine tested was that passed four to eight hours after the test dose. If an overflow of ascorbic acid from the tissues into the urine occurred it was presumed that the tissue requirements of vitamin C were being met. If, on the other hand, the administration of a massive dose of ascorbic acid produced no increase in the concentration of vitamin C in the urine it was suggested that the tissues were depleted of vitamin C. (The abstracter doubts the conclusions reached on the basis of these experiments.)

ROYSTER, University, Va.

HISTORICAL NOTES ON SOME VITAMIN DEFICIENCY DISEASES IN CHINA. T'AO LEE, Chinese M. J. **58**:314 (Sept.) 1940.

This communication is from the special number of this journal dealing entirely with the history of Chinese medicine. It comes from the division of Chinese, Peiping Union Medical College.

The author cites instances of nyctalopia (night blindness), which was recognized in the seventh century. It was called "sparrow blindness," because the sparrow "cannot see anything at night."

Beriberi was probably the disease mentioned in the book edited by Confucius in the fifth century B. C. Other references are found in the writings of early centuries, but in the seventeenth century there appeared the classic description, in "Ch'ao's General Treatise on the Etiology and Symptoms of Diseases," in which the disease was divided into much the same types as those used at present, namely, the endemic (wet), nonendemic (dry) and cardiac forms.

Mention of rickets in Chinese literature dates from remote times. In the book mentioned in the preceding paragraph, it was recognized that there was a disease which caused delay in teething and walking and resulted, as well, in the patient's having a large head and a patent fontanel. Therapy of the condition was unknown and did not advance as well as that of night blindness and beriberi, which were treated successfully in the early centuries.

NEFF, Kansas City, Mo.

Newborn

FACTORS INFLUENCING INFECTION IN THE NEWBORN. H. E. THELANDER, Arch. Pediat. **57**:685 (Nov.) 1940.

The following avenues of infection of the fetus and the newborn infant are given:

"I. Prenatal. 1. Via the maternal blood stream (spirochetes, bacteria, viruses).
2. Direct extension from the vagina to the uterus and fetus.

"II. At term direct extension due to early rupture of membranes or attempts at inducing labor.

"III. Postnatal. 1. Secondary to asphyxiation, narcosis, injury, etc.
2. Exposure to virulent organisms.
3. Rarely lack of normal immune mechanism."

ORR, Buffalo.

KERATOSIS DIFFUSA FOETALIS (REPORT OF CASE). JOHN JUDD SHIELDS and JAMES E. BOWMAN, Arch. Pediat. **57**:756 (Dec.) 1940.

A girl showed no abnormalities at birth except cutaneous lesions, which were somewhat suggestive of sclerema. The skin became dry and exfoliation became a dominant feature; so the diagnosis of dermatitis exfoliativa neonatorum was made. Though the definite microscopic changes characteristic of severe ichthyosis were absent or present to only a slight degree, the diagnosis of keratosis diffusa foetalis was made on the basis of the following observations:

1. The cutaneous lesions were present at birth and appeared to be regressive rather than spreading.

2. There was no spreading erythema preceding exfoliation, such as is described in cases of Ritter's disease.

3. The skin was thickened into parchment-like sheets, in contrast to the peeling of normal-appearing skin which occurs in Ritter's disease.

4. There were no blebs and no Nikolsky sign (a looseness of the outer cutaneous layers on rubbing).

5. Ectopian deformity of the external ears and clubbing of the fingers and toes were present.

The patient lived for three and one-half days.

The observations at autopsy are presented.

ORR, Buffalo.

ANEMIA OF THE NEWBORN WITH ERYTHROBLASTOSIS. GEORGE D. LYMAN, California & West. Med. **54**:64 (Feb.) 1941.

Lyman reports the case of an infant with anemia of the newborn who was apparently normal at birth but who became visibly jaundiced within twenty-four hours and began to show anemia on the seventh day of life. The proportion of normoblasts was as high as 5 per cent of the total red cells. The infant recovered after receiving four transfusions. The nature and the treatment of this condition are discussed, and a warning is sounded against giving too large or too frequent transfusions.

DAVIS, San Francisco.

MENINGITIS OF THE NEW-BORN DUE TO PSEUDOMONAS AERUGINOSA. A. E. ALLEN, Canad. M. A. J. **44**:288 (March) 1941.

A case of fatal meningitis of the newborn due to Pseudomonas aeruginosa is presented. Birth was premature. In addition, the infant had congenital atelectasis of the left lung and a patent foramen ovale. Examination of the brain at autopsy showed a considerable amount of material resembling coagulated serum in the subarachnoid space over the surface of the meninges. The ventricles were filled with a more purulent fluid, which on culture yielded a pure growth of Ps. aeruginosa. The same organism was isolated from the feces of the mother, who had severe diarrhea at the time of delivery.

MOORE, Omaha.

TREATMENT OF HYPOPROTHROMBINEMIA HAEMORRHAGICA NEONATORUM (HEMORRHAGIC DISEASE OF THE NEWBORN) WITH VITAMIN K. HENRY G. PONCHER and KATSUJI KATO, J. A. M. A. **115**:14 (July 6) 1940.

Twenty-two newborn babies were treated for hemorrhagic disease. They exhibited the typical symptoms of hematemesis, melena, omphalorrhagia, dermal hemorrhage, hematuria and cerebral symptoms prior to treatment. The prothrombin clotting time was determined before and after treatment by Kato's micromethod. The average time of two hundred and ten seconds before treatment was reduced to twenty-six seconds within two to six hours after administration of one of the synthetic preparations of vitamin K orally, intramuscularly or subcutaneously.

No transfusions were required, and only occasional parenteral administrations of fluids were employed.

HEERSMA, Kalamazoo, Mich.

LOCAL ACTION ON GONOCOCCIC BLENNORRHEA OF THE NEWBORN OF A SOLUTION CONTAINING A HIGH PERCENTAGE OF ACETYLSULFANILAMIDE. A. PILLAT, Wien. klin. Wchnschr. **40**:806 (Oct. 4) 1940.

Pillat reports that gonococcic blennorrhea of the newborn is curable in a remarkably short time by local treatment with 10 per cent acetylsulfanilamide. The treatment consists of dropping the drug in the conjunctival sac at half-hour intervals and irrigating the eyes, with physiologic solution of sodium chloride every quarter hour, night and day.

Bacteriologic examination of the solution used to wash the eyes after use indicates the progress of the treatment. The author has found that the gonococci disappear from the conjunctiva of the bulb and the lid in from one to two days. To insure a cure, it is recommended that the treatment be continued for twenty-four hours after the examination of the eye wash yields negative results.

The use of a 10 per cent or even of a 20 per cent solution of acetylsulfanilamide produces neither local nor general toxic efforts, and the preparation is well tolerated, even by newborn infants.

ABT, Chicago.

Acute Contagious Diseases

THE PRESENT STATUS OF WHOOPING COUGH IMMUNIZATION. LILLIAN KOSITZA, Arch. Pediat. **57**:731 (Nov.) 1940.

Of 478 immunized children, 90 were known to have been exposed to whooping cough and 15 contracted the disease. (Four of the 15 patients contracted whooping cough after exposure to unvaccinated siblings who had the disease.) Six other patients who contracted whooping cough either during the course of injections or within six weeks after completion of the course gave histories which indicated that with 1 possible exception their exposure occurred prior to the time the injections were started.

Of 173 controls, 61 were known to have been exposed to whooping cough and 41 contracted the disease.

For the vaccinated group the communicability rate was 16.6 per cent, while that for the unvaccinated group was 67.2 per cent.

ORR, Buffalo.

DIPHTHERIA MORTALITY IN LARGE CITIES OF THE UNITED STATES IN 1939. J. A. M. A. **114**:1875 (May 11) 1940.

Reports of the local health departments of the large cities of the United States in 1939 reveal a steady decline in deaths from diphtheria. In those cities 323 deaths occurred, a decrease of 160 from the figure for the preceding year. The rate was less than 1 per hundred thousand. The middle Atlantic and New England areas had the best records.

HEERSMA, Kalamazoo, Mich.

COMBINED (ACTIVE-PASSIVE) PROPHYLAXIS AND TREATMENT OF DIPHTHERIA OR TETANUS. GASTON RAMON, J. A. M. A. **114**:2366 (June 15) 1940.

Ramon discusses the results of administering both antitoxin and toxoid to patients with diphtheria or tetanus to produce permanent immunity. To patients suddenly exposed to diphtheria or to those receiving wounds which may lead to tetanus a single large dose of antitoxin is given and supplemented by four or five graduated doses of toxoid (anatoxin). Serologic tests show that "active, strong and permanent immunization can be induced by serotherapy combined with specific anatoxin vaccination."

HEERSMA, Kalamazoo, Mich.

CLINICAL USE OF IMMUNE HUMAN PLACENTAL GLOBULIN IN CHICAGO. HERMAN N. BUNDESEN, WILLIAM I. FISHBEIN, IRVING R. ABRAMS and RICHARD D. MILLER, J. A. M. A. **115**:104 (July 13) 1940.

Susceptible measles contacts were given injections of human immune (placental) globulin and human immune serum at varying intervals after exposure in the home. Ninety-five per cent of 678 children given globulin and 98 per cent of 299 immunized with serum either were protected or had a modified form of measles. Of a control group of 328 susceptible children who did not receive any injection, 83 per cent did not have severe measles. Prostration of those who became ill was most severe in the nontreated group. The studies as carried out did not establish the optimum time at which treatment should be given or the optimum dosage for immunization.

HEERSMA, Kalamazoo, Mich.

UNTREATED HUMAN STOOLS AS A SOURCE OF POLIOMYELITIS VIRUS. HOWARD A. HOWE and DAVID BODIAN, J. Infect. Dis. **66**:198 (May-June) 1940.

"The stools were put on ice immediately after collection and were kept in the icebox during a period of 1-24 hours which elapsed before preparation. As soon as feasible the specimen was ground up in a mortar with a quantity of distilled water sufficient to make a thick suspension. This material was then strained through cheese cloth to remove any remaining lumps. It was sealed in 10 cc. glass ampules, placed in a fluid-tight can and immersed in a mixture of alcohol and dry ice. All samples subsequently tested were thus subjected to one cycle of freezing and thawing. Before inoculation the specimen was resuspended in an additional quantity of distilled water, and spun slowly in a centrifuge to throw down the largest particles. The resultant supernatant fluid, which still contained large enough particles to resemble the original emulsion, was then inoculated intranasally into monkeys. Each animal received from 3 to 8 inoculations of 1 cc. per nostril lightly rubbed into the mucous membrane with a pipe cleaner. In some cases the inoculations were given on successive days; in others several days elapsed between the later inoculations.

"A simple technic is described for the demonstration of poliomyelitis virus in untreated human stools. Positive results were obtained in 10 out of 14 cases. During the first 5 days of the disease each of 7 stool specimens were found to contain virus."

TOOMEY, Cleveland.

GLOBULIN EXTRACT OF POOLED DISCARDED BANK BLOOD AS BLANCHING AGENT IN SCARLET FEVER. SAMUEL KARELITZ and STEPHEN S. STEMPIEN, J. Infect. Dis. **66**:240 (May-June) 1940.

"Pooled human serum globulins and placental globulin extracts are effective blanching agents in scarlet fever.

"Two of the human serum globulin preparations, nos. 48 and 49, were found to be more effective blanching agents than the horse serum antitoxin used routinely, even though the antitoxin content was lower.

"The pooled human serum needed for the preparation of the globulin extracts is now more readily available in hospitals because of the prevalent use of blood banks. Other sources of human globulins are suggested."

TOOMEY, Cleveland.

COMPARATIVE SUSCEPTIBILITY OF WILD AND DOMESTIC BIRDS AND ANIMALS TO THE WESTERN VIRUS OF EQUINE ENCEPHALOMYELITIS (BR. STRAIN) IN CALIFORNIA. BEATRICE F. HOWITT, J. Infect. Dis. **67**:177 (Nov.-Dec.) 1940.

This is an exhaustive piece of work on a timely subject. The author demonstrates where the virus may lie dormant.

"No virus was isolated from the brains of 43 wild animals and birds representing 144 different species.

"Gambel (Zonotrichia leucophys gambeli) and sparrows (Passer domesticus), quails (Lophortyx californica subsp.), juncos (Junco oreganus subsp.) and thrashers (Toxostoma lecontei lecontei) were all susceptible to intracerebral inoculation of the Br. strain of equine virus, even to a dilution of 10^{-6} for the first 3 species.

"The Richardson squirrel (Citellus richardsonii subsp.), cotton (Sigmodon hispidue texianus and eremicus) and kangaroo rats (Dipodomys heermanni subsp.) and six species of wild mice (Rheithrodontomys megalatus, Microtus montanus, Microtus californicus, Microtus mordax, Peromyscus truei and Peromyscus maniculatus) succumbed to 10^{6} and 10^{7} dilutions, respectively. Wood-rats (Neotoma fuscipes), puppies and 2 species of wild rabbits (Sylvilagus bachmani subsp. and Syl. audubonii) were also susceptible.

"Domestic fowl varied in their reactions to the virus, ducks and young turkeys usually succumbing to 10^{-4} dilution, pigeons and young chicks to 10^{-6} or $^{-7}$, respectively. Leghorn pullets and old hens were the most resistant of all barnyard fowl tested, the resistance varying more with the age than the locality or the presence of neutralizing antibodies.

"Frogs were unaffected by the virus.

"All birds resisting one intracerebral inoculation, even of highly dilute virus, were immune to a second stronger dose and most of them developed neutralizing antibodies in 5 to 7 days, which if weak were enhanced after the second injection.

"Virus could be recovered irregularly from the blood of inoculated fowl, even though they failed to show clinical symptoms of the disease.

"Neutralizing antibodies may appear in the serum of resistant fowl very soon after inoculation of virus and may also be present at time of or before death."

If, as has been shown, the mortality from equine encephalomyelitis for infants and children is about 80 per cent and the disease can be carried by mosquitoes or blood-sucking insects, the dangers from the wild birds and animals serving as reservoirs for the virus of the disease become readily apparent.

TOOMEY, Cleveland.

ATTEMPTS TO TRANSMIT THE VIRUS OF ST. LOUIS ENCEPHALITIS TO NEWLY HATCHED CHICKS. S. EDWARD SULKIN, CARL G. HARFORD and J. BRONFENBRENNER, J. Infect. Dis. **67**:252 (Nov.-Dec.) 1940.

"It is apparent from the results recorded in this paper that in spite of the most favorable circumstances, attempts to establish either apparent or inapparent infection with encephalitis virus in the newly hatched chicks were unsuccessful. It, therefore, appears doubtful that the chick could serve as a reservoir of the virus in nature.

"Whether or not there was any temporary increase of the amount of virus in the brains of the chicks during early passages cannot be determined with certainty from our data but it does appear likely that a limited degree of regeneration may have taken place. It is unlikely that the virus recovered from the brain of the chick after 5 passages could have represented carrying over of the original inoculum, because of the great dilution to which it was subjected during five successive passages. Moreover, the last experiment suggests that the original virus could not have retained its activity for the duration of these passage experiments (20 days) at the body temperature of young chicks."

TOOMEY, Cleveland.

MEDICAL PROGRESS. COMMUNICABLE DISEASES: CARDIOVASCULAR DISEASE IN DIPHTHERIA. CONRAD WESSELHOEFT, New England J. Med. **223**:57 (July 11) 1940.

Malignant diphtheria continues to claim many lives in the early stage, owing to the fact that antitoxin is not given in the first hours. From a clinical point of view, the term "malignant" may apply to any grave toxemia during the mem-

branous stage. Lowering the cough reflex with opiates is to be strictly avoided in the membranous stage. The best supportive measures consist of the vigorous administration of antitoxin, together with intravenous injections of 10 per cent solutions of dextrose (100 to 500 cc., according to the age of the patient). The use of insulin in conjunction with dextrose has been shown to be ineffective. Suction, intubation or tracheotomy may be necessary. If no obstruction is present the profound toxemia causes death. The heart poisoned by diphtheria is unusually susceptible to the action of digitalis, and block may be induced. The administration of camphor in oil, caffeine or coramine (a 25 per cent solution of pyridine betacarbonic acid diethylamide) has been found to be futile.

The promptness with which antitoxin is administered may prevent, delay or modify the manifestations of cardiovascular damage. Myocarditis is the outstanding pathologic feature and is present in most cases when circulatory failure occurs. The earlier the signs of myocarditis the graver the prognosis. The earliest signs of myocarditis are evident in the electrocardiogram. Like gallop rhythm, heart block may come and go, but its presence implies much greater danger than does the gallop. The advent of marked block usually precedes signs and symptoms of circulatory failure. A lowering of the tone of the sympathetic control is sometimes accompanied by marked lowering of the white blood cell count with relative lymphocytosis. Myocarditis is oftener only a contributory cause of death, the commonest cause being vasomotor paralysis. In a few hours the patient may be dead, or this condition may continue for several days and then lead to sudden fatal termination or to recovery. One type of myocarditis which occasionally occurs in the very toxic form of diphtheria is that associated with the formation of a thrombus. True vegetative endocarditis in the course of diphtheria is an extremely rare phenomenon. A mild but disturbing cardiovascular disorder may occur late in convalescence in some cases of diphtheria, namely, a curious irritability of the pacemaker which often results in an evening tachycardia persisting for three to eight weeks.

The pathologic changes observed in early circulatory failure in diphtheria are due to overwhelming toxemia and sometimes include dilatation of the heart. The term "myocarditis" is often used loosely to denote circulatory failure.

Hoyne and Welford found that the mortality rate in cases in which myocarditis was present was 75 per cent in patients under 5 years of age, 54 per cent in those from 6 to 10, 50 per cent in those from 11 to 15 and 43 per cent in those over 15. It was found that in cases of the simple tonsillar form of diphtheria the mortality rate was only 11 per cent, as compared with 54 per cent when the membrane had spread to the uvula and pharynx and 70 per cent when it had also spread to the nose.

There is logic in the use of pitressin (betahypophamine) when the blood pressure is low. It has a longer and more powerful action than epinephhine has. The use of an abdominal binder and the raising of the foot of the bed, as recommended by Harding, seemed particularly helpful. Warmth should be supplied in cases in which the patient's color becomes alabaster and the skin cold. The only measure which has consistently reduced the mortality in hospitals is the vigorous intravenous administration of solutions of dextrose in all cases of advanced diphtheria. All patients with severe diphtheria with evidence of myocarditis should be kept in bed for six to eight weeks, and those without electrocardiographic or clinical signs of myocarditis for four or five weeks. GENGENBACH, Denver.

IMMUNIZATION AGAINST DISEASE IN INFANTS AND CHILDREN. H. AUBREY WHITE, New Orleans M. & S. J. **93**:236 (Nov.) 1940.

The author gives a brief summary of the presently accepted ideas in regard to immunization against disease.

Sauer's vaccine is recommended for immunization against pertussis and of the various immunizing procedures this is advised to be used first. Standard doses are given.

For immunization against diphtheria the use of toxoid, alum-precipitated toxoid or combined alum-precipitated diphtheria and tetanus toxoids is advised for infants and for young children. For older children administration of toxin-antitoxin is advised.

Vaccination against smallpox is suggested as the last of the immunization procedures to be carried out, preferably at the end of the first year.

BERKLEY, Los Angeles.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **55**:2337 (Dec. 20) 1940.

There was a seasonal rise in the number of cases of influenza to 6,313 for the period of Nov. 3 to Nov. 30, 1940. The incidence in California and Arizona was above the expected average. The incidence of measles was also above average in the middle Atlantic, east north central and south central regions. The number of cases of poliomyelitis continued to decline but was still 55 per cent above the median for 1935 to 1939. The incidence of all other diseases was below average. The average mortality from all causes was 11.4 per thousand, as compared with the average for 1935-1939 of 11.3.

SANFORD, Chicago.

CEREBROSPINAL MENINGITIS. THE USE OF SULPHONAMIDE DERIVATIVES IN PROPHYLAXIS. R. W. FAIRBROTHER, Brit. M. J. **2**:859 (Dec. 21) 1940.

The author notes that there is an increased prevalence of this condition during wartime. The use of sulfanilamide and its derivatives in treatment has brought about a marked decrease in the mortality rate, a shortening of the duration of the disease and a great reduction in the incidence of sequelae. There is no generally accepted routine for the control of cerebrospinal meningitis, since even the prophylactic administration of these drugs is not of established value. The routine for the study of cerebrospinal fluid is outlined, as is the technic of nasopharyngeal swabbings, which the author thinks is important for studying the throat and handling prophylactic measures. An analysis of data from 51 cases of cerebrospinal meningitis follows. He thinks that there is no definite value in intensive prophylaxis because the effects of the disease on the human body are determined by the virulence of the meningococcus and the resistance offered by the host.

ROYSTER, University, Va.

ALUM-PRECIPITATED TOXOID IN DIPHTHERIA: DURATION OF IMMUNITY AFTER ONE-SHOT METHOD. F. C. FARAGÓ, Lancet **2**:68 (July 20) 1940.

In this paper the results of a two year study carried out in Hungary are reported. Schick tests were done on 22,129 children inoculated one to five years previously. The results were analyzed separately, those for children of preschool age (2 to 6 years) and those for school children (7 to 11 years). In the preschool group 16,435 Schick tests were done, of which 85.8 per cent gave negative reactions; in the school are group 5,694 Schick tests were done, of which 88.8 per cent gave negative results. The author concludes that the results in the two groups indicate that adequate immunity developed after one injection and that this lasts for a sufficiently long period under the epidemiologic conditions now prevailing in Hungary.

LANGMANN, New York.

THE PREVENTION OF ACUTE SPECIFIC FEVERS. JOHN C. G. LEDINGHAM, Practitioner **145**:91 (Aug.) 1940.

The author particularly stresses the importance of completing what may be called the primary sensitization to the antigens of smallpox, diphtheria and whooping cough before the close of the first year of life and of reenforcing the immunity so produced by administration of single small doses when the child has

reached school age. He also recommends the simultaneous immunization against diphtheria and pertussis by the administration of alum-precipitated diphtheria toxoid and pertussis vaccine.

GELSTON, San Francisco.

WHOOPING COUGH. JOSE MARTINHO DA ROCHA, Arch. de pediat. **12**:1 (Oct.) 1939.

The author considers that too little attention is paid in Brazil to this malady and its results. He points out that while in other countries deaths from whooping cough are diminishing, in Brazil they are constantly increasing. He considers lack of prophylaxis, malnutrition and contracting the disease at an early age the predominating direct causes of this situation. Of his own 322 patients, 60 died, 30 of them from pulmonary involvement (22 from bronchopneumonia, 2 from pneumonia, 5 from empyema and 1 from bronchitis); 38 of those who died were under 1 year of age and most of them had poor economic backgrounds and bad nutrition.

He considers that the measures for the diagnosis of whooping cough are chiefly clinical and that the results of bacteriologic, immunologic and hematologic investigations are of doubtful value because they are inconstant.

After making a thorough study of the pulmonary and mental complications of whooping cough and the features of the experimentally produced disease, he concluded that the peculiar cough is produced by the action of toxins on the fauces and larynx or on the central nervous system itself and that a lack of clinical symptoms of involvement of the nervous system is of no significance because degenerative and inflammatory lesions can be demonstrated in the absence of such symptoms.

SOTO, Habana, Cuba.

DIPHTHERIA IN THE ARMY OF ARGENTINA. JUAN F. R. BEJARNO, Rev. méd. latino-am. **25**:1003 (June) 1940.

The incidence of diphtheria increased from 1932 to 1936 and since then has not diminished appreciably. The number of cases suggests that the attempts to vaccinate against the disease have failed. The variability of the virulence of diphtheria bacilli through the years, the occurrence of other infections which lower the patient's resistance and the dose and the effectiveness of the immunizing agent used are discused in relation to the prevalence of the disease. It is advisable to omit giving the Schick test to a man entering the army and proceed with vaccination; the effectiveness of the vaccination should be checked every four months. The government should pass a law requiring immunization against diphtheria.

DWYER, Kansas City, Mo.

PREVENTION OF COMMUNICABLE DISEASES DURING SCHOOL AGE. J. SIEGL, Med. Klin. **36**:536 (May 17) 1940.

The author discusses the subject under two headings.

1. Exposition prophylaxis consists in combating of micro-organisms, isolation of patients and avoidance of contact of exposed children during the time for development of secondary cases. The problem is complicated by the factor of carriers. In some diseases the carrier state is not recognizable.

2. Disposition prophylaxis consists of passive and active immunization and of promoting nonspecific resistance. The latter can be accomplished by proper nutrition and judicious "hardening."

SIEMSEN, Chicago.

WHAT TREATMENT IN ADDITION TO SEROTHERAPY IS MOST EFFECTIVE IN TOXIC DIPHTHERIA? ELSBETH SCHENK, München. med. Wchnschr. **87**:784 (July 19) 1940.

From May 1939 to March 1940 a total of 700 patients with diphtheria were admitted to the City Hospital in Krefeld, Germany. About 10 per cent of the patients had toxic diphtheria. It is emphasized that in many of the cases,

especially those of the toxic type, the correct diagnosis was not made early enough by the practicing physician. For the 75 patients with toxic diphtheria the fatality rate was 47 per cent. In addition, in 50 cases in which the course was protracted there were extensive paralyses, and in 10 of these paralysis of the muscles of respiration developed and the patient died. Daily injections of a preparation of the vitamin B complex (betaxin) and administration of strychnine in increasing doses for two weeks gave good results in the cases in which paralysis occurred. Among 22 patients who received the preparation containing vitamin B complex alone there were 7 deaths. Of the 9 who received only strychnine, 2 died. A third group of 19 patients were given both strychnine and the vitamin preparation from the time of admission, and only 1 died. The survivors recovered completely from the paralysis. The author advises the addition of 5 to 10 cc. of "prontosil" (asosulfamide [?]) to the first dose of serum.

BRAHDY, Mount Vernon, N. Y.

THIS YEAR'S MEASLES EPIDEMIC. HEDWIG GERBE and H. ECKE, München. med. Wchnschr. **87**:851 (Aug. 9) 1940.

In recent years measles has been a mild disease which most children survive, except the weaklings and those with rickets. This year, however, there has been an epidemic of a different and very severe kind of measles. The incidence of complications among hospitalized patients was as follows: otitis media, 72 per cent; mastoiditis, 12 per cent; sinus thrombosis, 2.5 per cent, and pneumonia, 40 per cent (demonstrated by roentgenogram or autopsy). One reason for the severity of the epidemic may be that many persons from thinly populated rural sections have settled in the industrial centers.

BRAHDY, Mount Vernon, N. Y.

SCARLET FEVER IN CHINESE INDIGENOUS MEDICINE. YU YÜN HSIÜ, Chinese M. J. **58**:284 (Sept.) 1940.

The translations from early Chinese writings were made by Peter G. Mar.

It seems that scarlet fever did not exist in China in ancient and medieval times. Yeh T'ien Shih, who lived in the early part of the Ch'ing dynasty, left the first known records of cases in China. He lived during the period from 1662 to 1722 A. D.

Sometime after the year 1733 in a description of the disease it was stated that it could be transmitted from one person to another, that the eruption on the patient's skin had an appearance somewhat similar to that of finely embroidered silk and that the patient's throat was ulcerated, swollen and painful.

The author reviews the various names given the diseases in Chinese literature, the theories held by ancient Chinese about its etiology and the mention made of various symptoms and of treatment. It was suggested that "should the elder brother break out with this rash, administer the medicine to the younger brothers, or better still, send them to live elsewhere. . . ."

The author cites 93 references to scarlet fever in the old Chinese literature.

NEFF, Kansas City, Mo.

Acute Infectious Diseases

INTRATHECAL ADMINISTRATION OF TETANUS ANTITOXIN. WARFIELD M. FIROR, Arch. Surg. **41**:299 (Aug.) 1940.

After reviewing the several methods for treating clinical tetanus the author stated that the treatment is in an uncertain and unsatisfactory state. Animal experimentation was undertaken to determine the most successful method of administering tetanus antitoxin. Dogs were given lethal doses of tetanus toxin filtrate. Fifty-three hours later the animals were divided into groups according

to the severity of their symptoms and were given 680 American units of tetanus antitoxin per kilogram, either intravenously or intracisternally. It was noted that intracisternal administration of antitoxin is more effective than intravenous in curing early, moderate and well developed general tetanus, for of 36 dogs treated by intracisternal injections only 3 died whereas 19 of the 25 treated by intravenous injections died. The superiority of intracisternal injections in curing severe or far advanced tetanus is not apparent in this experiment. Experiments were also conducted to determine whether there is any difference in efficiency between antitoxin given intracisternally and that given in the lumbar region.

It is made clear in the paper that these experiments in themselves do not warrant the use of intracisternal injections for patients, but when considered with the reports of some well controlled clinical studies they furnish a strong argument for the employment of this form of treatment.

KAISER, Rochester, N. Y.

COCCIDIOIDOMYCOSIS. RELATIVE VALUES OF COCCIDIOIDIN AND TUBERCULIN TESTING AMONG CHILDREN OF THE SAN JOAQUIN VALLEY. JULIET E. THORNER, California & West. Med. **54**:12 (Jan.) 1941.

Two hundred and sixty-seven children selected at random from the patients attending the pediatric clinic of the Kern General Hospital, located in the San Joaquin Valley, where coccidioidomycosis may be said to be endemic, were tested simultaneously with 0.1 mg. of Koch's old tuberculin and 1.0 mg. of coccidioidin. It was found that there was a noticeably higher incidence of positive reactions to coccidioidin as compared with positive reactions to tuberculin as the length of residence in the county increased. Of the patients with less than one year's residence, 25 per cent reacted positively to coccidioidin and 32 per cent to tuberculin. Of those with ten or more years' residence, 76 per cent reacted positively to coccidioidin and 25 per cent to tuberculin. This survey confirms previous reports of the relatively benign as well as the universal, nature of the primary, or early, stage of the disease as it occurs in the San Joaquin Valley and makes it evident that the progression into the later and severe granulomatous stage occurs only when tissue and lymphatic resistance are overcome and generalized dissemination takes place via the blood stream, a rare occurrence.

DAVIS, San Francisco.

STUDIES IN THE SKIN TEST FOR COCCIDIOIDAL INFECTION: I. THE PREPARATION AND STANDARDIZATION OF COCCIDIOIDIN. R. A. STEWART and FRANCES KIMURA, J. Infect. Dis. **66**:212 (May-June) 1940.

"The specificity of the skin test cannot be determined until there is an accepted procedure for the preparation of coccidioidin and a standard strength for routine testing. The contradictory statements in the literature concerning the specificity of the skin test can be attributed to the lack of standardized coccidioidins of comparable potency.

"A simple method for the preparation of coccidioidin is described. A standard test dose has been defined in terms of skin units. The skin unit is an arbitrary but practical unit for the standardization of various coccidioidins. The skin unit may be determined upon guinea pigs or human cases of coccidioidal infection. The active substance responsible for the skin test is relatively heat stable and is dialyzable. It is probably a polysaccharide.

"Attention is again directed to the fact that there may be more than one immunologic species of coccidioides.

"The inadequacies of the generic concept of Coccidioides and the species name of 'immitis' are pointed out."

TOOMEY, Cleveland.

THE RESULTS OF ACTIVE IMMUNIZATION OF HUMAN BEINGS WITH A MIXED HEAT-KILLED VACCINE OF B. TYPHOSUS, BR. ABORTUS AND BR. MELITENSIS. JOHN A. KOLMER, AMEDEO BONDI JR. and ANNA M. RULE, J. Infect. Dis. **67**:258 (Nov.-Dec.) 1940.

"1. A heat-killed vaccine carrying 1,000 million B. typhosus, 1,000 million Br. abortus and 1,000 million Br. melitensis per cc. was administered subcutaneously to 29 normal adults in doses of 0.5, 1.0 and 1.0 cc. at weekly intervals.

"2. The vaccine was very well borne with reactions comparable to those following the administration of typhoid-paratyphoid vaccine.

"3. About 96% showed the production of agglutinin for B. typhosus and all for Br. abortus.

"4. All showed the production of immune opsonin for Br. abortus.

"5. The serums of 40% showed the presence of some protective antibody for B. typhosus before immunization while 83% showed the presence of protective antibody after immunization.

"6. The serums of about 17% showed some protective antibody for Br. abortus before immunization while the serums of 79% showed protective antibody after immunization.

"7. The serums of about 14% showed some protective antibody for Br. melitensis before immunization while the serums of 100% showed protective antibody after immunization.

"8. Immunization with the mixed heat-killed vaccine did not appear to produce allergic sensitization of the skin to brucellergen.

"9. Under the circumstances it is possible that vaccination of human beings with a mixed heat-killed typhoid-brucella vaccine is worthy of clinical trial for simultaneous immunization against typhoid and undulant fevers as a substitute for the usual typhoid-paratyphoid vaccine."

TOOMEY, Cleveland.

THE RESULTS OF ACTIVE IMMUNIZATION OF MICE AND RATS WITH HEAT-KILLED VACCINES OF BR. ABORTUS AND BR. MELITENSIS. JOHN A. KOLMER, AMEDEO BONDI JR. and ANNA M. RULE, J. Infect. Dis. **67**:268 (Nov.-Dec.) 1940.

"Mice actively immunized with subcutaneous injections of heat-killed vaccines of Br. abortus and Br. melitensis produced agglutinins and serum protection antibodies for the Brucella.

"Of 29 mice immunized with a heat-killed vaccine of Br. abortus and inoculated intra-abdominally with virulent Br. abortus, 16 or 55.2% survived. Of 29 additional immunized mice inoculated with virulent Br. melitensis 16 or 55.2% likewise survived. Of 28 mice immunized with a heat-killed vaccine of Br. melitensis and inoculated intra-abdominally with virulent Br. melitensis, 22 or 78.6% survived. Of 30 additional immunized mice inoculated with virulent Br. abortus, 16 or 53.3% survived, whereas of 17 unvaccinated control mice inoculated with Br. abortus none survived as likewise with 17 unvaccinated controls inoculated with Br. melitensis.

"Of 24 rats immunized with a heat-killed vaccine of Br. abortus and inoculated intra-abdominally with virulent Br. abortus, 15 or 62.6% survived while of 12 inoculated with Br. melitensis, 7 or 58.3% survived. Of 24 rats immunized with a heat-killed vaccine of Br. melitensis and inoculated intra-abdominally with virulent Br. melitensis, 22 or 91.7% survived while of 12 inoculated with Br. abortus, 8 or 66.6% survived. Of 16 unvaccinated control rats inoculated with Br. abortus 3 or 18.8% survived while of 16 inoculated with Br. melitensis none survived."

TOOMEY, Cleveland.

THE IN VITRO ACTION OF IMMUNE SERUM ON THE LARVAE AND ADULTS OF TRICHINELLA SPIRALIS. JOSÉ OLIVER-GONZÁLEZ, J. Infect. Dis. **67**:292 (Nov.-Dec.) 1940.

"The action of specific immune and hyperimmune serums from rats, guinea pigs and rabbits was tested in vitro on laryae and adults of Trichinella spiralis. In all of the immune and hyperimmune serums precipitate formed in large masses around the mouth of the larvae and was associated with immobilization, disintegration and death of many of the larvae. In addition to the oral precipitate, anal and vulval precipitates were formed around the adults. The vulval precipitate seemed to obliterate the opening and may be the mechanism whereby the escape of the embryos is prevented in immune serums.

"The time at which precipitates appeared varied according to the degree of immunization. In the serum from the hyperimmune animals precipitates appeared earlier and were denser than in the serum from immune animals. Inactivated serum was as effective as unheated or complemented serum.

"No precipitates were formed around the larvae or adult worms when placed in normal or in anti-Cysticercus-crassicollis serum.

"Serum from rabbits immunized with saline suspensions of powdered larvae apparently caused the death of over 50% of the larvae, but had little or no effect on the adults.

"Emphasis is laid upon the probable role of specific antibodies in acquired immunity to Trichinella spiralis." TOOMEY, Cleveland.

Chronic Infectious Diseases

EXTRAGENITAL TRANSMISSION OF SYPHILIS. GRADIE R. ROWNTREE and JAMES ROBERT HENDON, J. A. M. A. **115**:117 (July 13) 1940.

Five cases of syphilis in one family are reported. The disease was transmitted by kissing from the oldest boy, 19 years old, to the younger children. Two of the oral lesions were at first mistaken for lesions of minor cutaneous conditions (impetigo and thrush). HEERSMA, Kalamazoo, Mich.

SYPHILIS OF THE BONES IN INFANCY: SOME POSSIBLE ERRORS IN THE ROENTGEN DIAGNOSIS. W. A. EVANS JR., J. A. M. A. **115**:197 (July 20) 1940.

Several cases are reported illustrating the possible errors in the roentgen diagnosis of this condition. Diagnostic difficulties are accentuated by the present day early detection and treatment of maternal syphilis. Unless the disease is acquired early in utero (in the fifth month) roentgen changes may not be evident until the age of 2 or 3 months, since from four to six weeks is required after the infection of the fetus for osseous lesions to be produced. Disturbances of nutrition or growth may produce epiphysial lines or periosteal thickening. Also, early rickets, fracture, tuberculosis or other infections may produce periosteal shadows.

Even an early positive reaction to a test on the infant's blood may not prove the presence of syphilis unless it persists and increases, and a negative reaction may become positive after a few months. Observations should be close, so that any progress of the disease may be forestalled. HEERSMA, Kalamazoo, Mich.

THE COMPARATIVE VALUES OF CERTAIN MEDIUMS FOR THE ISOLATION OF BOVINE TUBERCLE BACILLI. ALFRED G. KARLSON, J. Infect. Dis. **67**:1 (July-Aug.) 1940.

"Tuberculous lesions from naturally infected cattle were cultured on glycerinated and nonglycerinated forms of four mediums. Bovine tubercle bacilli were isolated on the mediums not containing glycerin more frequently than on mediums containing it. The colonies were larger and appeared about a week earlier than

on glycerinated mediums. A medium made by adding the yolk of one egg to 150 cc. of melted and cooled beef extract agar gave satisfactory results. There was no advantage in using potato extract or meat infusion for the agar base. Since glycerin is demonstrated to inhibit the development of the bovine tubercle bacillus on original isolation it is recommended that nonglycerinated mediums as well as glycerinated be used in attempting isolation of tubercle bacilli from materials which might contain the bovine type of the tubercle bacillus.

TOOMEY, Cleveland.

THE PREVENTION OF PULMONARY TUBERCULOSIS. R. C. WINGFIELD, Practitioner **145**:92 (Aug.) 1940.

It is now generally accepted that pulmonary tuberculosis can and should be detected in its preclinical, symptomless stages by the use of mass roentgen examinations. By such examinations it should be possible to detect the potential sources of future infection and so treat them that they may never become actual sources of infection. Such a scheme, successfully handled, should mean the steady dwindling of the number of patients with positive sputum, not to zero but to such a low level that they will be communally harmless.

To make mass roentgen examinations extensive enough to be of practical value means enactment of laws and an apparent infringement of personal liberty, but with the help of such persons as public and private educational authorities, public service employment authorities, officers of insurance companies and large employers of labor, public opinion might be educated to appreciate the necessity and the advantage of such a procedure. In this connection it must be noted that the "contact" work of dispensary services, which should lead the way in this direction, leaves much to be desired, especially since it is often suggested that repeated familial exposure must be one of the gravest danger spots.

GELSTON, San Francisco.

DISCUSSION ON INTRATHORACIC TUBERCULOSIS IN CHILDHOOD. Proc. Roy. Soc. Med. **33**:619 (Aug.) 1940.

N. B. Capon made the following statements, which have been proved beyond dispute:

"(1) Intrathoracic tuberculous infection is common in childhood and infancy; it is usually contracted from adults who are in immediate and fairly prolonged contact with the child.

"(2) In many cases the early infection causes only slight ill-health and may be difficult to diagnose with certainty.

"(3) Many infants recover satisfactorily from the primary infection, especially if they are removed from infection at an early stage; but when the disease progresses until it is recognizable by ordinary clinical methods the outlook is serious, especially in infants under two years.

"(4) The most valuable special methods of examination are: (*a*) The search for *B. tuberculosis* in material obtained from the throat or from the stomach. (*b*) Testing for sensitivity to tuberculo-proteins. . . . (*c*) Radiography. . . .

"In the examination of a private patient who is suspected of tuberculous infection, it is wise to explain to the child's relatives the difference between tuberculous infection and tuberculous disease before the investigations are undertaken; and in some cases, where the relatives are obviously neurotic, it may be necessary to be guided entirely by the results of ordinary clinical examination; for the stigma of suspected tuberculosis is harmful to a child's progress under these special circumstances. The obvious danger of this course is that further contact with an infectious adult might continue.

"Two main clinical difficulties have to be faced:

"(1) To decide on the most suitable treatment for the child with extensive intrathoracic tuberculosis whose general health . . . is good. . . .

"(2) The assessment, especially from the prognostic point of view, of pulmonary changes which at their beginning are non-tuberculous, though they are undoubtedly secondary to tuberculosis: e. g. collapse of a lobe, and compensatory emphysema.

"The prevention of intrathoracic tuberculosis in childhood is still the most perplexing aspect of this subject. . . . tuberculo-phobia should not be encouraged by lectures and writings intended to educate the lay public."

R. Lightwood summed up his discussion as follows:

"Though statistical evidence in the form of follow-up studies is not sufficient to prove the point, it is probable that general treatment of primary tuberculosis in its early stage is justified, and the majority of clinicians support this view. Treatment in hospital is indicated more for social and economic than medical reasons. The child with primary tuberculosis is best treated at home or boarded out under good hygienic conditions, otherwise hospital accommodation must be provided, and this raises difficulties, particularly in infants. The tuberculosis authorities should pool their resources, and by joint action provide special accommodation for infants and children in co-operation with the children's hospitals."

Drs. B. Wood and G. G. Kayne also took part in the discussion.

WILLIAMSON, New Orleans.

BILATERAL ARTIFICIAL PNEUMOTHORAX FOR PULMONARY TUBERCULOSIS TWO YEARS AFTER TREATMENT WAS COMMENCED. BERYL D. CORNER, Proc. Roy. Soc. Med. **33**:626 (Aug.) 1940.

An 11 year old girl was brought to the hospital because of enuresis in July 1937. Her mother had died of pulmonary tuberculosis in 1936. A roentgenogram of the patient's chest showed nothing abnormal in the middle zone on the right. Admission was advised but refused, and the patient was lost sight of. In January 1938 she was admitted to the emergency surgical ward with acute vulval abscess. The pyrexia failed to subside after adequate drainage, and signs of consolidation were detected in the upper lobe of the right lung. Tubercle bacilli were present in the deposit from stomach washings. The patient was kept at absolute rest for two months, at the end of which time a roentgenogram showed evidence of cavitation in the right lung, and the temperature failed to settle at a normal level. Artificial pneumothorax was induced in May 1938. Mottling became more definite in the left midzone and the temperature was still elevated; so left artificial pneumothorax was induced in September 1938. Good collapse was maintained until September 1939, when fluid developed bilaterally, and the upper lobe of the left lung subsequently became adherent. It was noticed that a considerable amount of calcification was taking place in the collapsed lung. In May 1940 the patient was afebrile, no tubercle bacilli were detected in the stomach washings and guinea pig inoculations gave negative results. WILLIAMSON, New Orleans.

A STUDY OF TUBERCULOSIS AMONG STUDENTS AND NURSES; MORBIDITY AMONG NONALLERGIC SUBJECTS. J. TROISIER, M. BARIETY and P. NICO, Rev. de la tuberc. **5**:888, 1940.

As a result of their studies of tuberculous infection among students and nurses in Paris the authors have become convinced that the incidence of morbidity among nonallergic subjects greatly exceeds that among the allergic. This fact established, the rational procedure in the prevention of such morbidity would be to render the nonallergic subjects allergic. This end may best be brought about by the use of BCG. They favor the administration of 0.1 mg. intradermally. If the subject remains nonallergic after a reasonable time the dose should be repeated. It is

necessary for protection that allergy be established. This allergy should be maintained by subsequent inoculations if necessary. It is only by this means that the nonallergic adolescent may be forearmed against tuberculosis of moderate virulence.

EUGENE SMITH, Ogden, Utah.

ALLERGY AND RESISTANCE IN VACCINATION WITH BCG; NEW ARGUMENTS IN FAVOR OF THE EFFICACY OF THE METHOD OF VACCINATION OF CALMETTE AND GUÉRIN. R. CHAUSSINAND, Rev. de la tuberc. **5**:916, 1940.

Most authors who have studied the action of vaccination of infants with BCG. agree that this measure does not confer immediate resistance against virulent forms of infection. Against milder forms of infection, however, the resistance may be effective. It has also been demonstrated that about 11 per cent of infants so vaccinated will retain their resistance against tuberculosis for a period of about two years after the primary vaccination and will remain nonallergic, as shown by a positive reaction to the injection of BCG. Allergy is not synonymous with resistance, since it is possible for resistance to exist without allergy. The author's observations bear this out. Subcutaneous revaccinations seem to augment previously acquired resistance to tuberculosis even though the allergy produced is slight and fleeting. The resistance of the organism to tuberculosis appears to increase in proportion to the number of benign infections which it has been able to surmount, independent of the state of allergy.

Thirty infants who were vaccinated with BCG and remained nonallergic were carefully followed up. In spite of intimate and prolonged contact with a source of infection, clinical and roentgen examinations proved them absolutely free from tuberculous infection. It is inconceivable that during such intimate contact bacilli did not gain admission to the infants' bodies. One must conclude that in certain subjects vaccinated with BCG virulent tubercle bacilli comport themselves as inoffensive parasites which are unable to fix themselves in the body and are susceptible to elimination by ordinary means.

EUGENE SMITH, Ogden, Utah.

TWO CASES OF BILATERAL SPONTANEOUS DISLOCATION OF THE LENS IN CONGENITAL SYPHILIS. B. SZINEGH, Klin. Monatsbl. f. Augenh. **103**:230 (Aug.) 1939.

Two sisters, aged 10 and 6 years respectively, had bilateral luxation of the lens into the anterior chamber and secondary glaucoma. The symptoms of the second eye of each girl developed independently from those of the first eye, in each case after headache, pain in the eye and vomiting. Their elder brother, aged 12, had no ocular symptoms, and his Wassermann reaction was negative, whereas this reaction was strongly positive for the girls. Two abortions occurred between the birth of the boy and those of the girls. The history prompts the author to consider the ocular disturbances of the two girls as the result of congenital syphilis. (By an error in the original article the age of the "second child" is given as 10 years and that of the "third child" as 16 years, which evidently should be 6.)

K. L. STOLL. [ARCH. OPHTH.]

Diseases of the Nose, Throat and Ear

PRESENT STATUS IN THE TREATMENT OF ACUTE OBSTRUCTIVE INFECTIONS OF THE LARYNX, TRACHEA AND BRONCHI. H. R. LITCHFIELD, Arch. Pediat. **57**:717 (Nov.) 1940.

Twenty-nine cases are reported; only 2 deaths occurred. Fifty per cent of the patients were infants. Cultures of material from the throat yielded a variety of organisms, including Streptococcus haemolyticus, Micrococcus catarrhalis, Staphylococus aureus and Haemophilus influenzae.

Treatment consisted of laryngoscopic and bronchoscopic examinations with removal of mucus and, when the infection was severe, tracheotomy. Further treatment consisted of restoration of fluids, inhalations of steam and administration of oxygen.

ORR, Buffalo.

SULFANILAMIDE AND SULFAPYRIDINE IN THE TREATMENT OF ACUTE LARYNGO-TRACHEO-BRONCHITIS. R. R. MACGREGOR, Canad. M. A. J. **44**:48 (Jan.) 1941.

In 80 per cent of the author's cases streptococci were cultured from material from the throat. In 1 case of rapidly fatal termination pure cultures of Staphylococcus aureus were obtained from material taken from the larynx and the bronchial tree.

A portion of the summary reads as follows:

"Thirteen cases of acute laryngo-tracheo-bronchitis are reported. Nine cases were treated with sulfanilamide and four with sulfapyridine [2-(paraaminobenzenesulfonamido)-pyridine]. The usual standard dosage was used. As an adjunct blood transfusion was given in all cases on admission to hospital, and the child maintained in an atmosphere of intense humidity. . . . Of the 13 cases 2 died—one in the admitting room of the hospital. The other child, ill for three days, was moribund on admission and died in three hours, the parents refusing tracheotomy. . . ."

Medical treatment to be effective must be given before serious obstruction takes place; so early diagnosis is imperative.

MOORE, Omaha.

OBSERVATION ON 793 CASES OF ACUTE PURULENT OTITIS MEDIA WITH CHEMOTHERAPY IN 396 CASES. WESLEY C. BOWERS, J. A. M. A. **115**:178 (July 20) 1940.

Bowers analyzes data for 793 patients with otitis media treated during the past three years. About half of them were children. He concludes that chemotherapy reduces the duration of discharge by 50 per cent and the number of mastoidectomies by 50 per cent. The principal organisms cultured from material taken at operation for mastoiditis were Streptococcus haemolyticus (52 per cent), nonhemolytic streptococcus (10 per cent), pneumococcus group III (5 per cent) and staphylococcus (15 per cent).

There were no deaths in the cases in which there were no complications on admission of the patient and 2 in those with complications.

Bowers warns against using chemotherapy without removing the focus of infection or after uncomplicated mastoidectomy. A confused clinical picture may result when the drug is used during treatment. There were some recurrences when treatment was discontinued early.

HEERSMA, Kalamazoo, Mich.

THE TREATMENT AND PREVENTION OF DEAFNESS IN CHILDREN. J. E. BORDLEY, South. M. J. **33**:1159 (Nov.) 1940.

The author believes that children of early school age should have a careful examination of the hearing, as well as a general physical examination, if preventable impairment of hearing is to be controlled. Otoscopic, nasopharyngoscopic and audiometric examinations should be carried out. The perception of high tones, especially, should be tested.

The immediate eradication of infected lymphoid tissue should be undertaken whenever it is found to involve the eustachian tubes. Allergic manifestations should be corrected. Simple tonsillectomy and adenoidectomy are often not enough and should not be performed unless there are definite indications, because in many cases they do not remove the cause of the difficulty in hearing.

These measures in combination with careful treatment of acute infections of the middle ear and the mastoid with such drugs as sulfanilamide and sulfapyridine

(2-[paraaminobenzenesulfonamido]-pyridine) and, when necessary, conservative surgical procedures offer untold possibilities for the prevention of deafness in later life. All children with any signs of impairment of hearing should have periodic check-ups.

SCHLUTZ, Chicago.

Diseases of Lungs, Pleura and Mediastinum

ACUTE EMPYEMA THORACIS IN CHILDREN LESS THAN THREE MONTHS OF AGE. L. A. HOCHBERG and M. STEINER, Arch. Pediat. **57**:641 (Oct.) 1940.

In this communication the authors report their observations in the cases of 19 children with empyema who were less than 3 months of age; autopsy was performed in each case.

In all of the cases reported complications occurred, which in conjunction with the pneumonia and empyema present contributed to the patient's death. The complications were often so distributed that one might infer that a septic state existed at the same time.

Of the 19 cases reported, empyema was diagnosed before death in 9, or 48 per cent. In the remaining 52 per cent the condition was unrecognized until autopsy.

The chief causes for failure to recognize the empyema before death were:

1. The primary disease and its associated complications were so severe that they obscured or masked the presence of empyema.

2. The presence of empyema was suspected but was not confirmed clinically because of the short period during which the patient was in the hospital.

3. The amount of purulent exudate was too small to be observed clinically.

Bacteriologic studies of the pleural exudate were made in 12 cases. Staphylococci were observed in 8 (67 per cent), streptococci in 3 (25 per cent) and pneumococci in 1 (8 per cent) of the cases.

In the cases presented empyema may have been the result of (1) metastasis to the pleura, (2) pulmonary infection with secondary contamination of the pleural cavity, (3) extension of infection from the wall of the chest inward to the pleura or (4) subdiaphragmatic infection, either extending through or perforating the diaphragm.

ORR, Buffalo.

PNEUMONIA IN CHILDREN: TREATMENT WITH SULFAPYRIDINE. E. EARL MOODY and E. G. KNOUF, California & West. Med. **53**:116 (Sept.) 1940.

Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was used in the treatment of 126 children with pneumonia who were under 14 years of age. This group included approximately half of the patients seen during the period of study, and they seemed to have pneumonia of the most toxic type. The authors note that the incidence and the severity of pneumonia in general were less during this period than in former years. Of the 126 patients, 99 had lobar pneumonia and 27 bronchopneumonia. Pneumococci of a wide variety of types were found in 59 per cent of the cases. Sulfapyridine was given on the basis of 1 to 1.5 grains per pound (0.06 to 0.09 Gm. per 0.5 Kg.) of body weight per day, in six equal doses; treatment was given for two to twelve days (for five days or less in 83 per cent of the cases). The temperature had reached normal in forty-eight hours in 84 per cent of the cases (within twenty-four hours in 59 per cent), and in those cases in which it remained elevated for longer than six days there was some complication which the drug did not affect. There was only 1 death (0.8 per cent mortality) in the entire series. The authors are enthusiastic about the therapeutic results, but they caution that the drug is toxic and dangerous and advise careful control of all patients to whom it is given.

DAVIS, San Francisco.

SPONTANEOUS PULMONIC INTERSTITIAL AND MEDIASTINAL EMPHYSEMA IN AN INFANT. JOHN H. FISHER, Canad. M. A. J. **44**:27 (Jan.) 1941.

The case reported is that of a full term, normally delivered, white, female infant who weighed 7 pounds 15 ounces (3,600 Gm.) at birth.

About three and one-half hours after birth the baby became very cyanotic, and a blood-tinged froth exuded from her mouth. Administration of oxygen was of no avail; cyanosis increased, and the infant died five hours and forty-five minutes after birth.

Autopsy showed pulmonic and mediastinal emphysema. It is considered that the emphysema resulted from overinflation of the alveoli, which produced multiple rupture and escape of air into the perivascular sheaths.

MOORE, Omaha.

TREATMENT OF PNEUMONIA IN CHILDHOOD. R. R. STRUTHERS, Canad. M. A. J. **44**:271 (March) 1941.

This study concerns observations on 219 patients admitted to the Children's Memorial Hospital, of Montreal, Canada, between Oct. 1, 1938 and March 31, 1940. For 203 patients the recorded data were sufficiently detailed to be included in this review.

All of the patients were treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). The average dose for all patients was 1.39 grains per pound (0.08 Gm. per 0.5 Kg.), for those who had toxic symptoms 1.09 grains (0.065 Gm.) and for those who had complications 1.05 grains (0.063 Gm.).

The average level of the drug in the blood after forty-eight hours' administration was 6.3 mg. per hundred cubic centimeters, with a range of 1.02 to 10.70 mg.

On the basis of his experience, the author suggests an average dose of 0.75 grain (0.048 Gm.) per pound per twenty-four hours instead of the usual dose of 1 grain (0.065 Gm.).

The mortality rate for the whole group was 2.5 per cent.

Thirty-two per cent of the patients had complications and 36.4 per cent some signs of toxicity due to the drug.

The urine should be examined every two days for blood and crystals of sulfapyridine.

MOORE, Omaha.

TREATMENT OF BRONCHOPNEUMONIA UNDER THE AGE OF ONE YEAR. A. MORTON GILL, Brit. M. J. **2**:900 (Dec. 28) 1940.

The author comments that for infants under 1 year of age with bronchopneumonia the mortality rate is usually about 90 per cent. The disease is not common in this age group except as a complication of the acute exanthems. The author states ". . . it is difficult to collect enough cases treated in hospital to enable conclusions to be drawn as to the efficacy of methods of therapy. . . . I have selected those in whom the prognosis should have been poor—i. e., infants in the first year of life with extensive and widely disseminated patches of consolidation." He has made an abstract of data from these cases and gives an outline of the therapy used.

He concludes that the usual predisposing cause of the bronchopneumonia was the contracting of a common cold. The prognosis is usually poor, especially for those infants who have intense cyanosis or repeated convulsions and those who relapse after first responding to treatment. In his series there were 4 deaths; consequently the mortality rate was 36 per cent, which is much better than rates previously reported for this age group. The treatment consisted of the administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) as follows: 0.125 Gm. at four hour intervals to patients up to 3 months of age and 0.25 Gm. at four hour intervals to patients from 3 months to 1 year of age; the initial dose was invariably double the routine dose.

Oxygen was administered in an oxygen tent. Two types of tents are described. Feedings were given at two hour intervals, day and night, feedings of half the normal or usual strength being used. The author thinks that the fluid intake is of greater importance than the caloric intake. Chloral hydrate is administered by mouth to insure sleep and to allay restlessness. The nursing is important. He states that the comparatively low mortality rate of 36 per cent is due to this routine.

ROYSTER, University, Va.

PULMONARY CIRCULATION AND THE ATTACK OF BRONCHIAL ASTHMA. LORENZO GALINDEZ and F. A. MACIEL CRESPO, Rev. méd. latino-am. **25**:967 (June) 1940.

The newer conception of the pathogenesis of bronchial asthma emphasizes alterations in the pulmonary circulation rather than in the musculature of the bronchioles. Pulmonary stasis is frequently present during an attack of asthma. Other allergic manifestations, such as urticaria and vasomotor rhinitis, can be explained on the basis of circulatory changes, and the physiology and the pharmacology of the pulmonary circulation lend support to this view. Epinephrine exerts more influence on bronchospasm than atropine because it affects not only the bronchi but the blood vessels, while atropine affects only the bronchi.

DWYER, Kansas City, Mo.

INTRAMUSCULAR ADMINISTRATION OF ANTIPNEUMOCOCCAL SERUM IN INFANTS AND CHILDREN. LAMBERT KRAHULIK, VICTOR RUDOMANSKI and GEORGE CUNNINGHAM, J. Pediat. **15**:650 (Nov.) 1939.

Patients seriously ill with pneumococcic pneumonia seen over a period of one year were treated with intramuscular administration of antipneumococcus serum. A total of 64 infants and children were treated; 18 were under and 46 were over 2 years of age. The infants were given 60,000 to 100,000 units of serum and the older children 80,000 to 200,000 units. A comparative study of these 64 treated patients and a group of infants and children seen over a period of ten years and not treated showed a marked decrease in the duration of the illness, a reduction in the incidence of complications and a fall in mortality rate for the treated patients. The administration of the serum by the intramuscular route was found to be a safe method, for no severe reactions occurred.

RAUH, Cincinnati.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE WINTER VOMITING DISEASE. JOHN ZAHORSKY, Arch. Pediat. **57**:666 (Oct.) 1940.

During February 1940 an epidemic of this disease occurred in St. Louis. It is estimated that fully 3,000 children were attacked by it within a period of two weeks. In June 1929 the author reported a similar type of epidemic and suggested the name hyperemesis hiemis for the syndrome. Similar epidemics have been observed in other communities throughout the country.

The disease is described as beginning abruptly; older children complain of abdominal pains for one or two days preceding the acute attack. Vomiting is the first symptom, the gastric contents being ejected with force. Sometimes symptoms of collapse, that is, extreme pallor, prostration and feebleness of the pulse, ensue rapidly. The vomiting continues for one or more days. Nothing is retained by the stomach. Violent retching and the expulsion of mucus are frequent.

An important diagnostic symptom is diarrhea, which begins soon after the vomiting. The stools are light colored and have a very offensive odor. Colicky pains accompany the diarrhea and persist for several days after it has ceased. Microscopic examination of the stools shows that they do not contain cells.

Fever in cases of the uncomplicated form of the disease is not high; the pulse rate is rapid and the respiratory rate increased. Acidosis may develop in some cases. Dehydration sometimes occurs in infants.

In discussing the etiologic factors, the author still adheres to the conclusions expressed in his previous article, namely, that the winter vomiting disease, which appears sporadically or epidemically, should be separated from the group of symptoms called grip. In support of this theory he states that typical cases

occur in explosive epidemics and the physician is overwhelmed by the number of patients needing medical attention. Another important sign is the putrefactive nature of the stools and the toxic symptoms. One observation made during the epidemic of February 1940 was that the bacterial counts on grade A pasteurized milk from one of the largest St. Louis dairies were considerably higher during the epidemic than during the previous month, as is shown in the tabulation.

Bacteria per Cc. of Milk January 1940	Bacteria per Cc. of Milk February 1940 (During Epidemic)
2,600	45,000
1,200	70,000
28,000	28,000
2,400	10,000
250	1,300
5,200	11,000
1,800	23,000
5,000	200
5,000	14,000
200	12,000
900	2,000
59,000	210,000
22,000	39,000
55,000	
5,700	
26,000	
13,000	

The prognosis is good except for young infants; only 1 death was reported during the St. Louis epidemic.

ORR, Buffalo.

CONGENITAL ATRESIA OF THE ESOPHAGUS: A STUDY OF THIRTY-TWO CASES. THOMAS H. LANMAN, Arch. Surg. **41**:1060 (Nov.) 1940.

This condition is discussed in detail, and 32 cases are reported. Of particular interest are the characteristic and striking symptoms. "They are attacks of choking and cyanosis occurring in the first few hours of life, and almost invariably these attacks are aggravated whenever any fluid is offered the infant. Attempts to swallow fluid are followed by immediate regurgitation and are usually accompanied with evidence of aspiration of fluid into the air passages, shown by choking, coughing and cyanosis." These symptoms should suggest the diagnosis. The taking of a roentgenogram without the use of a contrast medium is helpful. Frequently a fistula is associated with the atresia, so that the giving of barium sulfate by mouth is accompanied by great danger and should never be done.

Unfortunately, the surgical treatment of the anomaly has not been successful, for all 30 of the patients who were operated on died. The author feels, however, that improved technic and greater experience will eventually result in a successful outcome of direct anastomosis of the esophagus.

KAISER, Rochester, N. Y.

MANAGEMENT OF ADVANCED APPENDICITIS IN CHILDHOOD. W. D. GATCH, R. E. GERY and FELIX BALLENGER, J. A. M. A. **114**:1839 (May 11) 1940.

Of 357 cases of appendicitis in children which the authors reviewed, there was perforation of a gangrenous appendix in 135, in all but 16 of which immediate appendectomy was done. Delay in performing the operation because of abscess formation caused no mortality, while 1 patient who was operated on died of endocarditis and bacteremia. In 18 similar cases in which operation was not performed there were 3 deaths from generalized peritonitis.

The authors explain the effects of generalized peritonitis on the basis of loss of protein and hemoconcentration, which they combat with lavage, fluids and blood transfusions. Meticulous surgical technic in removing the appendix so that there is no spreading of the infection and institution of drainage are described as vital.

HEERSMA, Kalamazoo, Mich.

GALLSTONES IN CHILDREN. VICTOR B. SEIDLER and ELIZABETH BRAKELEY, J. A. M. A. **114**:2082 (May 25) 1940.

The cases of 432 children with disease of the gallbladder have been reported. If the idea that this condition is a disease of adults were discarded, an ever increasing number of occurrences of the condition would be recognized in spite of the decrease in typhoid fever as a possible causative factor. Mechanical stasis due to congenital or lymphatic obstruction may be associated. The typical case of a 10 year old girl is reported; there was a history of pain, intermittent jaundice, rheumatic fever and suspected tuberculosis of six years' duration. Roentgen examination showed evidence of gallstones, and operation disclosed obstruction by an enlarged lymph node. She had an uneventful recovery.

Besides emphasizing the necessity for considering disease of the gallbladder in making the diagnosis, the authors mention the possibility of its being associated with appendicitis.

HEERSMA, Kalamazoo, Mich.

PECTIN-AGAR FOR DIARRHEA IN INFANTS AND THE NEWBORN: A RATIONAL, SIMPLE AND EFFECTIVE TREATMENT. PHILIP J. HOWARD and CHARLES A. TOMPKINS, J. A. M. A. **114**:2355 (June 15) 1940.

This treatment of diarrhea consists of feeding a mixture of pectin, agar and dextrimaltose, cooked for ten minutes in milk. The effect of pectin, the active agent of the apple diet, is discussed in relation to its adsorbent properties and its detoxifying and healing effects. The agar adds bulk and is adsorptive. The dextrimaltose and milk supply a large amount of carbohydrate at a time when metabolism is speeded and ketosis imminent.

In 23 cases of enteritis of the newborn this regimen was used with excellent results, the number of days of diarrhea being shortened from the four to seven usual with standard treatment to one to six. The method is simple, practical and applicable to use in the home.

HEERSMA, Kalamazoo, Mich.

THE TREATMENT OF MEGACOLON WITH PARASYMPATHETIC DRUGS. JOHN L. LAW, J. A. M. A. **114**:2537 (June 29) 1940.

Fifteen patients with megacolon were treated with doses of 0.1 to 0.2 Gm. of acetylbetamethylcholine bromide. One patient died of bromide poisoning due to drug idiosyncrasy. Six of the patients had daily evacuations when given the drug and liquid petrolatum. Two of these patients were able to discontinue taking the drug after three and nine months respectively. The case of a patient who had dilatation of the colon, demonstrated by roentgen examination, malnutrition and abdominal distention even though she had daily evacuations is described.

HEERSMA, Kalamazoo, Mich.

INTRADERMAL INJECTION OF BACTERIUM NECROPHORUM IN PATIENTS WITH CHRONIC ULCERATIVE COLITIS. G. M. DACK, JOSEPH B. KIRSNER and LESTER R. DRAGSTEDT, J. Infect. Dis. **66**:261 (May-June) 1940.

"Patients with chronic ulcerative colitis are no more sensitive to intradermal injections with suspensions of killed Bact. necrophorum prepared from strains isolated from their own diseased colon than are healthy volunteers similarly tested with these same antigens. In both groups an inflammatory reaction develops which is nonspecific and to which antibodies are not developed."

TOOMEY, Cleveland.

INTRA-ABDOMINAL DIAGNOSIS. E. K. MACKENZIE, Edinburgh M. J. **47**:805 (Dec.) 1940.

A portion of this article deals with children. In writing about intussusception in infancy, the author urges the physician not to worry too much about differential diagnosis in this fulminating type of obstruction or he may fail to recognize in time the gravity of the condition. When life depends on a vital decision he thinks that the child should have the chance of possible benefit from operative intervention as long as the patient is in safe surgical hands.

Mackenzie devotes one page to the problem of diagnosing pyelocystitis in children. Typically, one finds that the patient is a girl with fever (unexplained at first), frequency of urination, with some discomfort and pus in the urine, which nearly always contains colon bacilli. Observing these symptoms will easily clear up the diagnosis for the worried general practitioner. The author has never seen a boy with the disease, but he believes that a routine examination of the urine should not be neglected in the case of a boy with unexplained fever.

NEFF, Kansas City, Mo.

TREATMENT OF HEPATOMEGALY IN CHILDREN. A. MORES, Kinderärztl. Praxis **11**:321 (Oct.) 1940.

A 7 week old infant had excessive enlargement of the liver with hypoglycemia. There was a normal blood sugar response to the administration of epinephrine. The edge of the liver was felt at the iliac crest. The spleen was not palpable. Within four weeks after roentgen treatment the liver shrank to practically normal size. A dose of 15 r was given through a copper filter, with the central ray directed to the anterior edge of the liver. Details of the mechanical factors are given in the article. The same dose was repeated after an interval of four weeks, and the enlargement had disappeared completely by the end of the next three weeks. The infant was seen again at the age of 6 months and was doing well.

Mores recommends this treatment in cases of disturbed glycogen storage or in steatosis of the liver.

HEYMANN, Cleveland.

Nervous Diseases

ENCEPHALITIS IN INFANTS AND CHILDREN CAUSED BY THE VIRUS OF THE EASTERN VARIETY OF EQUINE ENCEPHALITIS. SIDNEY FARBER, ALLEN HILL, MARION L. CONNERLY and JOHN H. DINGLE, J. A. M. A. **114**:1725 (May 4) 1940.

Eight cases of encephalitis in infants and children occurred during an epidemic caused by the virus of the eastern type of equine encephalitis. The cases were similar to those observed in epidemics caused by the viruses of the St. Louis and Japanese types of encephalitis, polioencephalitis, rabies and encephalitis lethargica.

The observations at autopsy in the 5 cases terminating fatally and the encephalograms in those in which recovery ensued were typical. There was a predominance of polymorphonuclear leukocytes in the cells in the spinal fluid; a count of 5,000 cells per cubic millimeter was recorded in 1 case. Residual changes were pronounced in the 3 patients who survived.

The diagnosis is difficult but may be established by serum neutralization tests or by virus transfer from autopsy material. There is no standard treatment.

HEERSMA, Kalamazoo, Mich.

THE SURGICAL TREATMENT OF LEAD ENCEPHALOPATHY, WITH PARTICULAR REFERENCE TO THE PREVENTION OF SEQUELAE. W. TRACY HAVERFIELD, P. C. BUCY and ANNA S. ELONEN, J. A. M. A. **114**:2432 (June 22) 1940.

Five patients with lead encephalopathy were treated by surgical decompression of the brain.

This condition should be suspected when a child shows signs of increased intracranial pressure without definite localizing signs. The patients reported on had

vomiting, irritability, paralysis and convulsions, anemia, basophilic stippling of the red cells, a lead line in the epiphyses and lead in the excreta.

Three of the 5 patients recovered. The only residuum noted was the moderate mental deficiency shown by the child whose disease was the most chronic.

It is felt that relieving the increased intracranial pressure may prevent subsequent residual paralysis, mental deficiency, convulsions and blindness.

HEERSMA, Kalamazoo, Mich.

PROPAGATION OF THE ST. LOUIS AND THE JAPANESE B. ENCEPHALITIS VIRUSES IN MOUSE TESTICLE. EDWIN H. LENNETTE and MARGARET G. SMITH, J. Infect. Dis. **66**:266 (May-June) 1940.

"The viruses of St. Louis and of Japanese B. encephalitis multiply with facility in the mouse testicle. After testicular injection both viruses attain within 3 days a concentration in the testicle comparable to that reached in the brain after cerebral inoculation. This high titer persists for a week or 10 days and then decreases, the virus disappearing about the 3rd week.

"The St. Louis virus has been maintained through 25 generations by testicular passage, the Japanese virus through 14 generations. In neither case has there been any observable diminution in the neurotropic character of the virus.

"The Japanese virus displays a much greater tendency to spread to the brain and to produce a fatal encephalitis following intratesticular inoculation than does the St. Louis virus. The former virus has been readily recovered from the brains of mice showing no symptoms when sacrificed 3 to 14 days after testicular inoculation, while similar attempts with the St. Louis virus have been consistently negative."

TOOMEY, Cleveland.

FAMILIAL LUMBOSACRAL SYRINGOMYELIA. C. VAN EPPS and H. D. KERR, Radiology **35**:160 (Aug.) 1940.

The appearance at the clinic of 2 or more members of 4 different families with trophic changes in the soft and bony tissues of the feet led Van Epps and Kerr to review the literature of similar cases. It is their belief that the various etiologic factors of the syndrome are of the developmental type and that the terms status dysraphicus myelodysplasia, syringomyelia and trophopathia pedis myelodysplastica all have some basis. They have classified their cases in the syringomyelia group and feel that the term "familial lumbosacral syringomyelia" is the best designation. To date there have been reported 54 cases, to which the authors now add 27 of their own, making a total of 81 cases. They made examinations in 19 of the 27 cases included in this report. Twenty-six of these cases occurred in 4 families, while in the other case the authors have been unable as yet to establish a familial tendency. Of the 19 cases in which examination was made, the feet showed calluses in 16, one or more ulcers in 17 and pain, usually slight, in 6. The knee jerks were normal in 18; the achilles tendon reflex was absent in 12, and plantar extension was absent in one or both feet in 9. Pallesthesia was impaired or lost in 16 cases; hyperkeratosis of the hands was present in 2 cases, and the skin of the hands was dry and thick in a third case. Roentgen examination of the feet showed osseous changes in 15 cases. These changes were trophic in character—absorption of bone, disintegration of joints, periosteal new bone and pathologic fractures. Soft tissue changes could also be seen. Roentgenograms of the lumbosacral portion of the spine convinced the authors that spina bifida occulta per se is not a necessary part of the syndrome. In 4 cases there were episodes of severe infection. In 1 case of chronic infection amputation below the knee was necessary. In only 1 case has there been a possible appearance of the condition in the fourth generation. One family showed an associated case of striate diplegia with athetosis. In the sporadic case there were unequal partial Argyll Robertson pupils, primary atrophy of the optic nerve and retrobulbar neuritis with slightly constricted fields. This case may be one of tabes, but the authors have included it because they have not

seen similar changes in the feet occurring in tabes and because these changes are typical of those in the familial groups. They reach the conclusion that the occurrence of chronic painless ulcers on the feet, especially when associated with roentgen evidence of neurotrophic changes in the bones and joints of the forepart of the foot, should lead to a study of the family history in a search for similar cases. Familial lumbosacral syringomyelia is one of the most frequent causes for such a syndrome. Irradiation of the lumbosacral cord appears to be the best available treatment.

J. A. M. A.

CHOREA OF INFECTIOUS ORIGIN. EDWARD F. REASER, South. M. J. **33**:1324 (Dec.) 1940.

The author summarizes his report as follows:

"Sydenham's chorea is a symptom-complex, exhibiting both physical and mental phenomena, caused by changes in the central nervous system due to the effects of the toxin produced by the etiologic agent of the disease known as rheumatism. This causative agent is presumed to be bacterial, but has not yet been demonstrated in its association with the rheumatic manifestations of polyarthritis, heart disease and chorea.

"The choreic displays are the results of either a pre-existing weakness of the nervous tissues as compared to the other tissues ordinarily involved or of a selective property of the toxin elaborated by a particular strain of the infective agent.

"Chorea, as a disease entity, appears in varying degrees of severity, ranging from restlessness and irritability to a state of helplessness, agitation, mental derangement and hyperpyrexia which may lead to death.

"Chorea usually offers a favorable prognosis both as to physical and mental symptoms."

SCHLUTZ, Chicago.

THE TREATMENT OF MENINGITIS DUE TO THE MENINGOCOCCUS, HAEMOPHILUS INFLUENZAE, PNEUMOCOCCUS AND STREPTOCOCCUS. D. G. HAMILTON, M. J. Australia **2**:342 (Oct. 12) 1940.

Since the introduction of sulfanilamide and its derivatives the mortality from meningococcic meningitis in the Royal Alexander Hospital for Children has been reduced from 50 per cent in the preceding ten years to 13.4 per cent, that from influenzal meningitis from 98.4 per cent in the preceding seven years to 64 per cent, that from streptococcic meningitis from near 100 per cent to 60 per cent and that from pneumococcic meningitis from 100 per cent to 85.7 per cent.

Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) appears to be of more value than sulfanilamide in the therapy of meningococcic infections. The average age of the children who recovered from influenzal meningitis was a little over 7 years, and no child was less than 2 years old. The average age of those who died of this disease was a little over 2 years. The treatment for influenzal meningitis now recommended by Hamilton is large doses of sulfapyridine by mouth and specific influenza antiserum by intramuscular injection on the first day (because of possible septicemia) and by intrathecal injection each day until recovery is assured. Complement, given in the form of fresh human serum by intrathecal injection, seems to be of little value in the treatment of influenzal meningitis. For treating pneumococcic meningitis, which remains the most lethal of the common forms of purulent meningitis, vigorous administration of sulfapyridine is the most hopeful therapy yet available. For the treatment of streptococcic meningitis sulfanilamide is the drug of choice.

GONCE, Madison, Wis.

ACUTE TOXIC POLYNEURITIS. J. B. ATKINS, Proc. Roy. Soc. Med. **33**:626 (Aug.) 1940.

An 8½ year old boy was admitted to the hospital with a history of paresthesia of the fingers and toes of one month's duration and weakness of the hands and

feet with pain in the calves of two weeks' duration. There had been no previous illness.

On examination there were marked wasting and loss of power in the small muscles of the hands and feet, and foot drop was present. The biceps reflex and the knee jerk were graded 2 plus, and the other reflexes were diminished. There was muscle tenderness in the calves; there were bands of hyperesthesia to all forms of sensation at the knee and ankle, with diminished sensation below. Reaction of degeneration in the maximally wasted muscles was present. Examination of the cerebrospinal fluid showed 255 cells per cubic millimeter and 30 mg. of protein per hundred cubic centimeters. The sedimentation rate was 15 mm. in one hour. The reaction to a Schick test was negative. The boy showed steady improvement with physical therapy.

WILLIAMSON, New Orleans.

CEREBRAL ABSCESS DUE TO PFEIFFER'S BACILLUS—SIX YEARS AFTER PFEIFFER'S BACILLUS MENINGITIS. T. G. I. JAMES, Proc. Roy. Soc. Med. **33**:628 (Aug.) 1940.

The patient, aged 9 years, was admitted to the hospital in a lethargic state, with rigidity of the neck, a positive Kernig sign, right hemiplegia and slight papilledema. At the age of 2 years the child had suffered from influenzal meningitis, and Pfeiffer's bacillus was isolated from the cerebrospinal fluid. After recovery the child still had right hemiplegia. Lumbar puncture on this second admission yielded a clear fluid greatly increased under pressure; which contained 26 cells per cubic millimeter. A roentgenogram of the skull showed a calcified lesion in the left frontoparietal area. The patient became increasingly lethargic and a month later was unconscious. The left frontoparietal region was explored through a burr hole; a calcified area was found under the dura mater, and a large abscess was opened and 3 ounces (89 cc.) of pus obtained. Culture of the pus yielded Pfeiffer's bacillus. The child regained consciousness. Further treatment consisted in repeated aspirations of the abscess. The wound finally healed, and the child was free of symptoms apart from the right hemiplegia, which remained unchanged.

WILLIAMSON, New Orleans.

BRAIN SHOWING CEREBRAL HAEMORRHAGE IN A CASE OF SPONTANEOUS LABOUR. Proc. Roy. Soc. Med. **33**:736 (Sept.) 1940.

Prof. F. J. Browne showed the brain of a 4 day old child in which there was a clot 1½ inches (4 cm.) long in each lateral ventricle. The mother, aged 27, had previously had two miscarriages. During the third pregnancy the only abnormality noted was chronic hypertension, the blood pressure being 140 mm. of mercury systolic and 80 mm. diastolic. About the twenty-eighth week, however, there was a flare-up of symptoms, with increase of blood pressure, albuminuria and some edema. Nevertheless, the pregnancy continued until the end of the thirty-sixth week, when it was intended to terminate it by cesarian section. Since the fetus was small, it was decided to delay operation for at least another week. Five days later labor began, and the child, weighing 4½ pounds (2,041 Gm.), was born after the mother had had two or three pains. The child, judging by its weight, should have done well; but it had attacks of cyanosis, took its feedings badly and died on the fourth day. The cause of death was hemorrhage into both lateral ventricles.

WILLIAMSON, New Orleans.

TREATMENT OF JUVENILE TETANY WITH "A.T. 10" [DIHYDROCHOLESTEROL]. F. GERLÓCZY, Kinderärztl. Praxis **11**:350 (Nov.) 1940.

The case of a 14 year old girl with typical juvenile tetany is described. The level of calcium in the blood serum was 5.6 mg. and that of phosphorus 9.6 mg. per hundred cubic centimeters. The disease started with the first menstrual period. Administration of calcium and solution of parathyroid for two and a

half weeks produced no effect. Administration of a preparation containing 0.5 per cent dihydrocholesterol in a dosage of 1 or 2 cc. per day cured the patient within a few weeks. There was no relapse during the year that she was kept under observation.

HEYMANN, Cleveland.

PSYCHIC PHENOMENA AND FOCI OF SOFTENING IN ENCEPHALITIS. URSULA ZANDER, Ztschr. f. Kinderpsychiat. **7**:1 (May); 42 (July) 1940.

Two cases of acute epidemic encephalitis are discussed. The psychic symptoms which accompany acute encephalitis consist of (*a*) clouding of consciousness, (*b*) disturbances of affect, (*c*) automatism, (*d*) hyperkinesis, (*e*) epileptoid seizures and (*f*) muscle palsies. At times there may be generalized mild or severe phenomena indicative of a meningitic process.

JAHR, Omaha.

Psychology and Psychiatry

THE PREVENTION OF MENTAL ILLNESS. R. G. GORDON, Practitioner **145**:99 (Aug.) 1940.

The main preventive measures include genetic selection, antepartum hygiene, prevention of trauma, regulation of infection, maintenance of endocrine balance and prevention of emotional conflict. Also must be mentioned the reduction of economic stress, improvement in industrial conditions, diminution of the risk of accidents, establishment of shorter working hours (provided the subject is taught or learns to use his leisure), improvements in housing and abatement of noise.

It must not be thought, however, that all obstacles should be cleared from life, for to the strong person effort is the spice of existence. However, every one is not strong, and to the lamb shorn by physical illness, early mismanagement, break-up of the home or other accidents which he cannot prevent the wind must be tempered as much as possible.

GELSTON, San Francisco.

MOTOR AND PSYCHIC ADAPTATIONS OF HANDICAPPED CHILDREN. ROSA KATZ, Ztschr. f. Kinderpsychiat. **7**:17 (May) 1940.

This is a report of an experimental study the object of which was to determine the means by which handicapped children adapt themselves to the performance of daily tasks requiring full motor and mental equipment. Speech, writing and reading, for example, necessitate muscular and psychic activity.

Normal children were used for the investigation. They were divided into five groups, in each of which artificial "handicaps" were produced for the purpose of study, as follows:

In group 1 the children were asked to perform a task requiring two hands with one hand tied (for example, peeling a banana, threading a needle and opening and closing a bottle).

In group 2 the children were blindfolded and given such tasks as using a hammer, a needle or a pencil.

In group 3 the children were completely deafened by plugging the ears with a special preparation to exclude all sound and were requested to respond to sentences spoken to them.

In group 4 the children were given certain difficult sentences which they were required to understand and to repeat.

In group 5 the children were assumed to be unable to write conventionally and were instructed to express their thoughts in whatever manner they deemed best.

The results indicate that children are exceptionally clever in devising means to adapt themselves to handicaps. Even young children are capable of figuring out ways and means by which to carry out approximately an accepted routine.

The learning process operates, though naturally with more difficulty than in the case of the normal youngster without a handicap, and instinctively or otherwise the child somehow finds a solution to his problems.

JAHR, Omaha.

DEVELOPMENT OF CHILD PSYCHIATRY IN NORTH AMERICA. JACOB LUTZ, Ztschr. f. Kinderpsychiat. **7**:33 (July) 1940.

The rise of the mental hygiene movement and its effects on the development of the child guidance clinic are historically depicted. While in Europe child psychiatry was an outgrowth of the psychiatric clinics for the adult, the author states that in America the child guidance clinics found their roots in the efforts of such men as Healy, of Boston, Meyer and Kanner, of Baltimore, Plant, of Newark, N. J., Allen, of Philadelphia, and Schroeder, of Chicago. These physicians early became interested in juvenile delinquency and the possibility of its prevention through family guidance by the physician, the psychologist, the social worker and other persons or groups capable of aiding in the rehabilitation process.

JAHR, Omaha.

Diseases of the Genitourinary Tract

ADENOMYOSARCOMA OF THE KIDNEY (WILMS TUMOR). HERMAN L. KRETSCHMER, Arch. Surg. **41**:370 (Aug.) 1940.

The author reports the cases of 3 boys, aged 1½, 2½ and 7 years, with Wilms tumor. In the discussion of the symptoms of this tumor it is stressed that the tumor runs a relatively silent course. This is unfortunate for the patient, because in many cases treatment is sought too late to make surgical relief possible. Symptoms referable to the urinary tract are absent, with the possible exception of the rare cases in which hematuria occurs. Pain is a relatively uncommon symptom and occurs late in the course of the disease. Anemia and loss of weight are late manifestations, as are pressure symptoms. The first symptom usually noted by the parent is the presence of an abdominal tumor. The presence of an abdominal tumor in a child should lead to a tentative diagnosis of Wilms tumor, for it is the commonest of such tumors in children.

Methods used to establish the diagnosis should include a complete urologic study and roentgen studies, including examination of the chest. The author's procedure for treatment consists in a course of high voltage roentgen therapy followed by nephrectomy, after which another course of high voltage roentgen therapy is carried out.

KAISER, Rochester, N. Y.

CONGENITAL ANOMALIES OF THE URINARY TRACT, THE UNDERLYING CAUSE IN MANY URINARY INFECTIONS IN CHILDREN. ALLAN B. HAWTHORNE, Canad. M. A. J. **44**:152 (Feb.) 1941.

"A series of urinary infections in children has been reported. There were 61 in females and 24 in males. Of these, 40 were chronic in nature, 24 in girls and 16 in boys.

"Sixty per cent of these chronic infections persisted because of urinary stasis or obstruction caused by some congenital abnormality in the urinary tract.

"Among the remaining 40 per cent a certain number of the chronic infections in girls cleared up on treatment only after the removal of infectious foci elsewhere in the body."

MOORE, Omaha.

TECHNIQUE IN ESTABLISHING THE DIAGNOSIS OF GENITO-URINARY MALFORMATION. CHARLES E. SNELLING, Canad. M. A. J. **44**:269 (March) 1941.

The importance of diagnosing genitourinary malformation before damage to the kidneys occurs is stressed.

The following procedures are advised: (*a*) the taking of a complete history and performance of a thorough physical examination, (*b*) repeated urinalyses and (*c*) when indicated, special laboratory examinations, such as determination of the levels of nonprotein nitrogen and creatinine and tests of renal function.

Roentgenograms, such as a flat plate of the abdomen, a cystogram and a pyelogram, should be made.

In some cases cystoscopic examination and retrograde pyelograms are necessary.

MOORE, Omaha.

JUVENILE NEPHRITIS AND LEAD POISONING. Editorial, J. A. M. A. **114**:1753 (May 4) 1940.

In a large percentage of the 186 cases of chronic nephritis about which data are presented in the book entitled "Chronic Nephritis and Lead Poisoning," by L. J. Jarvis Nye, of Brisbane, Australia, the patient was a child. The patients lived in a certain region of Queensland, Australia. Gibson and Turner, physicians of Brisbane, investigated the condition endemic in this area. The houses of the poor inhabitants of this region had similar verandas, the railings of which were painted with white lead paint. Almost all of the affected children were nail biters, and it was deduced that dried flakes of the lead-containing paint lodged under the finger nails and were swallowed while the children played on the verandas. They had all the symptoms of lead poisoning and later showed signs of vascular nephrosclerosis.

HEERSMA, Kalamazoo, Mich.

THE TREATMENT OF PREPUBERAL VULVOVAGINITIS WITH A NEW SYNTHETIC ESTROGEN: PRELIMINARY REPORT. JOSEPH D. RUSS and CONRAD L. COLLINS, J. A. M. A. **114**:2446 (June 22) 1940.

Twenty-five children with gonorrheal vulvovaginitis, 20 months to 12 years of age, were treated with a synthetic estrogen (diethylstilbestrol). They were given 1 mg. three times daily in milk for one week or until the smears of material from the vagina were negative for gonococci and pus. Treatment for longer than one week was required in only 4 cases. The only positive smears found on repeated examination after discontinuance of therapy proved to be due to reinfection.

Photomicrographs of smears of material taken from the vagina and sections of the vaginal mucosa illustrate the effects of the drug.

HEERSMA, Kalamazoo, Mich.

THE EFFECT OF HORMONES ON THE UNDESCENDED TESTIS: AN EXPERIMENTAL AND CLINICAL STUDY. J. S. EISENSTAEDT, MAX APPEL and MAX FRAENKEL, J. A. M. A. **115**:200 (July 20) 1940.

The authors' experience with cryptorchidism leads them to feel that Browne's classification of the positions of the testes is the most nearly accurate. He divides them into three principal categories: (1) normal positions, from which the testis eventually will descend spontaneously; (2) undescended positions, in which the testis has been arrested in its normal course at some point from which there will be no normal descent, and (3) ectopic position, in which the testis has deviated from the normal direct line of descent.

Administration of large doses of chorionic gonadotropin has a harmful effect on the human testis, since it causes atrophy and produces adhesions. The authors' experiments showed consistent changes in the cryptorchid rat testicle after the treatment, the microscopic degeneration of the seminiferous tubular epithelium being particularly marked.

True undescended and ectopic testes are never brought down normally without surgical treatment, which has given good results in 87 per cent of the authors' cases.

HEERSMA, Kalamazoo, Mich.

THE SHORT PHENOLSULPHONEPHTHALEIN TEST OF RENAL FUNCTION. MILTON PLOTZ and MARGARETHE ROTHENBERGER, J. Lab. & Clin. Med. **26**:587 (Dec.) 1940.

The short, or thirty minute, phenolsulfonphthalein test was used on a number of patients. A 25 per cent secretion in fifteen minutes and a 35 per cent secretion in thirty minutes are considered normal. The authors feel that the two hour test has no advantage over the shorter one, ond they point out the ease with which this test can be done in one's office. GARD, Galveston, Texas.

THE INTRAVENOUS ADMINISTRATION OF SMALL DOSES OF CASEIN HYDROLYSATE TO NEPHROTIC CHILDREN AND ITS EFFECT UPON THE NITROGEN BALANCE AND PLASMA AMINO ACID LEVEL. LEE E. FARR, J. Pediat. **16**:679 (June) 1940.

"Four nephrotic children, two boys, aged 4 and 6 years, and two girls each aged 7 years, have been observed on a nitrogen balance study for fifteen consecutive weeks.

"The intravenous administration of amino acids as a casein hydrolysate caused flushing of the skin and a sensation of warmth. . . . No febrile reactions were encountered.

"Nitrogen given as intravenous amino acids was assimilated and retained as well as, or better than, similar amounts of nitrogen fed as protein. After amino acid injections, the capacity of nephrotic patients to assimilate high protein diets was markedly increased over that previously observed. Increased effects of amino acids were not obtained by the simultaneous administration of glucose.

"The injections had no effect upon the ratio of urea plus ammonia nitrogen to nonprotein nitrogen in the urine, plasma protein level, or fasting plasma amino acid level.

"In three of the four patients the administration of amino acid intravenously produced an increase in the urea clearance which persisted for from three to five months after injections had been discontinued." RAUH, Cincinnati.

ACACIA THERAPY IN A CHILD WITH NEPHROSIS. DOROTHY F. FALKENSTEIN and ROBERT L. JACKSON, J. Pediat. **16**:700 (June) 1940.

Reports in the literature on the use of acacia in cases of nephrosis have not been in agreement as to its effect. Some authors have reported good results following its use, and others have reported adverse effects from its use. Studies on human beings and on dogs showed that the administration of acacia resulted in a marked lowering of the level of protein in the serum, a deposition of acacia in the liver, bone marrow, lymph nodes, lungs, kidneys and spleen and only a transitory or slight effect on edema. Changes in the dextrose and galactose tolerance curves following the intravenous administration of acacia to dogs have been interpreted as evidence of damage to the carbohydrate and serum protein metabolic functions of the liver. Falkenstein and Jackson report a case of nephrosis in which a total of 705 Gm. of acacia was administered intravenously over a period of six months, with a drop in the level of protein in the serum from 4.7 to 1.5 Gm. per hundred cubic centimeters. The liver became enlarged, and the level of protein in the serum remained alarmingly low for many months. The patient was followed up over a period of six years. Death resulted from pneumococcic peritonitis, empyema and pneumonia. Autopsy revealed subacute glomerular nephritis with nephrosis. The deposits of acacia amounted to 50.3 Gm. in the liver, 2.85 Gm. in the spleen and 0.07 Gm. in the left kidney. Of the total amount of acacia administered, 7.55 per cent was recovered from the body organs six years later. During this period it had been impossible to increase

the patient's level of the serum protein to normal. The authors believe that ultimate recovery of the patient with nephrosis is dependent on his ability to restore the level of protein in the serum to normal and that acacia seems to hinder the synthesis of protein.

RAUH, Cincinnati.

CONGENITAL OBSTRUCTION OF THE BLADDER NECK. W. L. GRANTHAM and R. C. BUNTS, South. M. J. **33**:939 (Sept.) 1940.

The authors believe that the commonest causes of congenital obstruction of the neck of the bladder are valves, fibrosis and hypertrophy of the verumontanum.

In the treatment of this condition preliminary drainage must be carried out until there is stabilization of the renal and vascular systems. During this period of preliminary drainage fluids should be forced and secondary anemia, which is often present, should be treated.

Fibrosis, hyperplasia and hypertrophy of the outlet of the bladder are best treated, when possible, by transurethral resection with or without preliminary cystostomy. In many cases in which cystostomy has been advised for drainage treatment by removal of a wedge-shaped piece of tissue from the neck of the bladder through the suprapubic opening is feasible.

The prognosis depends entirely on the amount of damage which has taken place in the upper part of the urinary tract. If the patient can be seen before reflux of fluids has occurred the chances of obtaining a good functional and systemic result are excellent.

SCHLUTZ, Chicago.

THE GYNECOLOGICAL DISORDERS OF PUBERTY AND ADOLESCENCE. GERTRUDE DEARNLEY, Practitioner **145**:163 (Sept.) 1940.

Most of the gynecologic disorders of puberty and adolescence tend to improve, and most of them will respond to medical treatment, although it may take time.

Such disorders are due mostly to disturbance of function, although in some cases organic disease is present. The patient's type should be assessed, that is, whether she is young for her age, underdeveloped or precocious, obese or thin. The circumstances of her life, such as overstrain or incompatibility at home or overwork at school, should be taken into account. In all cases a general examination should be made as well as a pelvic examination per rectum.

The author discusses briefly, and rather inadequately, the subjects of leukorrhea, primary dysmenorrhea and amenorrhea and irregular periods associated with intervals of secondary amenorrhea and menorrhagia.

GELSTON, San Francisco.

GENITAL DYSPLASIA. A. J. WALKER, Proc. Roy. Soc. Med. **33**:626 (Aug.) 1940.

The patient, aged 2 years, was admitted to the hospital for determination of sex. On admission the child was normal in appearance except for genital abnormalities. The clitoris was about 1 inch (2.5 cm.) long and about ½ inch (1.3 cm.) in diameter and had a well defined glans. The external labia were slightly pigmented and wrinkled, like scrotal skin, and there were some well developed pubic hairs. A roentgenogram of the pituitary fossa was normal. Laparotomy was performed, and two small spindle-shaped ovaries, two fallopian tubes and a small uterus were discovered. There seemed to be no vagina. There was no enlargement of the adrenal region. The external sinus below the clitoris ended blindly. It was impossible to pass a probe into the bladder.

WILLIAMSON, New Orleans.

LATE HEREDITARY SYPHILIS OF THE TESTICLE. JUAN JOSE GAZZOLO, Rev. méd. latino-am. **25**:1367 (Sept.) 1940.

Syphilis of the testes is rarely observed before the age of 16 years. The case of a 14 year old boy is reported.

Other stigmas of syphilis, such as dental irregularities and parenchymatous keratitis, were present.

DWYER, Kansas City, Mo.

Diseases of the Ductless Glands; Endocrinology

THE PRESENT STATUS OF THE THYMUS GLAND IN PEDIATRIC PRACTICE. E. A. MORGAN, Canad. M. A. J. **44**:41 (Jan.) 1941.

The author reviews all of the various theories relating to the physiologic function and pathologic characteristics of the thymus gland.

A critical review of the arguments for and against the incrimination of the thymus as the cause of certain clinical symptoms shows that the implication of the gland is based on very scanty evidence and that the most suspicious symptoms can be much more logically and scientifically related to other known pathologic conditions.

There are still some occurrences for which there is no adequate explanation, such as the sudden death of a child following some slight injury.

MOORE, Omaha.

CORRELATION OF PHYSIOLOGICAL AND CYTOLOGICAL CHANGES IN THE NEUROHYPOPHYSIS OF RATS WITH EXPERIMENTAL DIABETES INSIPIDUS. I. GERSH and CHANDLER M. BROOKS, Endocrinology **28**:6 (Jan.) 1941.

The primary purpose of these experiments was to observe the gland cells of the neurohypophysis under various conditions, during the temporary and permanent phases of experimental diabetes insipidus and after hypophysectomy. The rat was the animal used in this study because the parenchymatous cells in the neurohypophysis of this animal are easily and precisely identified, as their cytoplasm contains characteristic lipid droplets. The distribution of these cells in the infundibular process and stalk corresponds precisely with the sites from which the antidiuretic substance can be extracted. Moreover, it was found that the gland cells hypertrophy when experimental evidence indicates that the store of active principle in the infundibular process is being depleted. Conversely, the gland cells become smaller when there is reason to believe that the antidiuretic substance is not being actively secreted.

The following theory seems to explain best the observations made regarding the severity of the diabetes insipidus produced and the atrophy and the hypertrophy of the various parenchymatous glandular cells of the neurohypophysis: The parenchymatous gland cells of the neurohypophysis are released from nervous control when the nerve fibers which innervate them are destroyed. In this state they atrophy. As part of the picture of paralytic secretion the less differentiated cells which are also denervated may then hypertrophy and subsequently atrophy through exhaustion. When the number of inactive, or atrophic, cells is large there is an attempt at compensatory hypertrophy. If this is successful and the remaining cells can secrete enough antidiuretic substance, the animal will show only the temporary phase of diabetes insipidus. If the hypertrophic cells are too few or the hypertrophy is not sufficiently great and the amount of antidiuretic principle secreted is below the physiologic level, the animal will suffer from a persistent, slightly excessive output of urine and intake of water. If the differentiated cells are too few and the hypertrophic cells secrete to the point of exhaustion permanent diabetes will ensue.

JACOBSEN, Buffalo.

RETARDATION OF MAMMARY INVOLUTION IN MICE BY INJECTION OF LACTOGENIC HORMONE. CHARLES W. HOOKER and W. LANE WILLIAMS, Endocrinology **28**:42 (Jan.) 1941.

Experiments utilizing suckling young and the substitution of chemical irritation for the effect of suckling have shown that stimulation of the nipple is a major factor in maintaining lactation and in preventing mammary involution in rats and mice.

The experiments on lactating mice isolated from their young reported on here show that animals receiving prolactin exhibited definite retardation in mammary involution. The average degree of involution in the treated animals was that normally resulting from four days' segregation from their young, when there actually had been seven days of segregation. The inhibition of involution manifested itself chiefly as maintenance of the lobular-alveolar and duct systems in a condition very similar to that present at parturition.

It is suggested that suckling prevents mammary regression and maintains lactation in mice by virtue of the stimulation of the nipples, which elicits a release of lactogenic hormone, which, in turn, maintains the mammary glands.

JACOBSEN, Buffalo.

INHIBITION OF MAMMARY GROWTH BY LARGE AMOUNTS OF ESTROGEN. W. U. GARDNER, Endocrinology **28**:53 (Jan.) 1941.

Experiments on mice, monkeys and dogs indicated that weekly injections of estradiol benzoate and estradiol dipropionate inhibited mammary growth.

JACOBSEN, Buffalo.

THE RELATION OF THE THYROID TO MAMMARY GLAND GROWTH IN THE RAT. SAMUEL L. LEONARD and RALPH P. REECE, Endocrinology **28**:65 (Jan.) 1941.

Thyroidectomy of young female rats, of spayed rats and of spayed rats treated with estrogen resulted in increased mammary development. In view of the known stimulating effects of thyroid treatment on mammary growth, the results of these experiments were unexpected.

A discussion of the possible mechanism is presented. JACOBSEN, Buffalo.

SKELETAL CHANGES IN RATS RECEIVING ESTRADIOL BENZOATE AS INDICATED BY HISTOLOGICAL STUDIES AND DETERMINATIONS OF BONE ASH, SERUM CALCIUM AND PHOSPHATASE. HARRY G. DAY and RICHARD H. FOLLIS JR., Endocrinology **28**:83 (Jan.) 1941.

Over 200 rats were treated with estradiol benzoate over varying periods and the effects on the skeleton studied by means of histologic, roentgenologic and chemical technics.

The evidence indicates that estrogen causes a decrease in the normal destruction of bony trabeculae just beneath the junction of cartilage and shaft. This increases the density of the epiphyses and apparently accounts for the increase in the concentrations of total bone ash. However, the total amount of bone is reduced, because of the decreased growth in length. JACOBSEN, Buffalo.

ADMINISTRATION OF RAT THYMUS TO PREGNANT RATS AND THE LACK OF EFFECT IN SUCCESSIVE GENERATIONS. M. W. BURRILL and A. C. IVY, Endocrinology **28**:94 (Jan.) 1941.

In 1934 Rowntree and his associates reported that daily treatment of rats with an extract of calf thymus caused an acceleration of growth and development in their offspring. It was found that with continued treatment the effect was enhanced in each succeeding generation.

Similar, but not identical, experiments were carried out by Burrill and Ivy. Treatment of pregnant rats through four successive generations with fresh rat thymus failed to produce a significant acceleration of growth and development in the offspring.

JACOBSEN, Buffalo.

PERMANENT AFTER-EFFECTS FOLLOWING MASCULINIZATION OF THE INFANTILE FEMALE RAT. JAMES T. BRADBURY, Endocrinology **28**:101 (Jan.) 1941.

An after-effect of masculinization of the infantile female rat by treatment with either chorionic gonadotropin or testosterone is continuous vaginal estrus.

The mechanism whereby treatment with androgens produces continuous estrus as an after-effect is not by the production of permanent ovarian damage. The results indicate that the permanent change probably occurs in the anterior lobe of the pituitary gland.

JACOBSEN, Buffalo.

THE GROWTH DEPRESSING EFFECT OF LARGE DOSES OF TESTOSTERONE PROPIONATE IN THE CASTRATE ALBINO RAT. H. S. RUBINSTEIN and M. L. SOLOMAN, Endocrinology **28**:112 (Jan.) 1941.

Testosterone propionate given in doses of 1 mg. daily (except Sunday) for from twenty-six to eighty days depressed the body length and weight of the castrate male albino rat to a still greater degree than that observed after castration alone. It is felt that this added depression represents a summation of the effects of castration plus the depression of pituitary function incident to overdosage with androgenic substance.

JACOBSEN, Buffalo.

CUTANEOUS VASCULAR AND PIGMENTARY CHANGES IN CASTRATE AND EUNUCHOID MEN. EDWARD A. EDWARDS, JAMES B. HAMILTON, S. QUIMBY DUNTLEY and GILBERT HUBERT, Endocrinology **28**:119 (Jan.) 1941.

The cutaneous vascularity and pigmentation of 4 castrated males (including a Negro) and 5 eunuchoid patients were studied before, during and after treatment with testosterone proprionate. Determinations were made with the aid of the Hardy recording spectrophotometer.

It is concluded that androgens have a profound influence on the vascularity and pigmentation of the entire human skin.

JACOBSEN, Buffalo.

THYROID MEDICATION DURING CHILDHOOD. LAWSON WILKINS, J. A. M. A. **114**:2382 (June 15) 1940.

Thyroid medication is valuable in the treatment of hypothyroidism of childhood whether the disease is manifested as cretinism or as juvenile hypothyroidism. The clinical picture of hypothyroidism is described, and the diagnostic value of evidence of retardation of bone growth and increase in blood cholesterol is mentioned. Treatment should be not only adequate to remove the clinical symptoms but sufficient to produce a fairly rapid change in the abnormalities disclosed by roentgen and laboratory studies. Mental retardation is the most refractory symptom, and all results are better the earlier treatment is begun.

Little can be said about the value of using thyroid in the treatment of other conditions except that good effects seem to have been achieved by giving it in conjunction with some types of pituitary preparation.

HEERSMA, Kalamazoo, Mich.

RECENT STUDIES ON THE DIAGNOSIS OF HYPOTHYROIDISM IN CHILDREN. LAWSON WILKINS, Pennsylvania M. J. **44**:429 (Jan.) 1941.

The author discusses structural and functional changes. He comes to the conclusion that these studies are only a beginning in the search for more specific and objective methods of measuring thyroid function and that exact criteria for

the diagnosis of thyroid deficiency cannot yet be stated. Most children with hyperthyroidism present characteristic clinical pictures, and elaborate biochemical studies serve only to confirm diagnoses already fairly obvious. In a few atypical cases or in cases in which the patient had previously been treated with thyroid, the studies have proved of considerable value in demonstrating clearly the presence or absence of thyroid deficiency.

LOGUE, Williamsport, Pa.

SPLANCHNECTOMY AND GRAVE DIABETES. V. BANET, P. P. NOBO and J. L. BOLADERES, Vida nueva **45**:389 (June) 1940.

The authors stress the fact that such a radical treatment as splanchnectomy is to be reserved for rare cases, in which the disease is of extraordinary gravity and resistant to treatment with insulin and, particularly, when there are complicating, stubborn local infections. The blood sugar curve is not immediately stabilized, and in fact immediately after operation there is a period of instability during which hypoglycemic shock is apt to be caused by much smaller doses of insulin than the patient had taken preoperatively. Extraperitoneal abdominal sympathectomy is recommended, and it is felt that in addition to stabilizing the blood sugar level the resulting vasodilatation and leukocytosis favor the eradication of the infection.

DIETRICH, Beverly Hills, Calif.

Diseases of Muscles, Bones, Joints and Lymph Glands

CONGENITAL ABSENCE OF THE SACRUM. I. M. ZELIGS, Arch. Surg. **41**:1220 (Nov.) 1940.

Two cases of this rare condition are reported. It is felt that this abnormality dates back to early embryonal life. Of particular interest to the clinician are the characteristic clinical features which are, in part, manifestations of the vertebral defect and, in part, manifestations of the neurologic lesion which almost inevitably accompanies it. The vertebral defect causes a flattening which replaces the normal convexity of the sacrococcygeal region and a flattening of the buttocks. There is also a shortening of the intergluteal fold and absence of the bony concavity of the sacrococcyx normally palpable on rectal examinations. The neurologic features result from involvement of the sacral or the lumbosacral plexus and include to a varying degree incontinence of urine and feces, atrophy and diminished muscle power of the lower extremities and associated deformities of the feet. Treatment consists of the usual orthopedic measures designed to correct the existing deformities of the lower extremities.

KAISER, Rochester, N. Y.

TREATMENT OF MUSCULAR DYSTROPHIES AND ALLIED CONDITIONS: PRELIMINARY REPORT ON USE OF VITAMIN E (WHEAT GERM OIL). SIMON STONE, J. A. M. A. **114**:2187 (June 1) 1940.

Seven patients with disturbances of muscle function were treated with vitamin E (wheat germ oil). The administration of vitamin B complex seemed to increase the benefit from this treatment. The 5 patients with muscular dystrophy were definitely benefited.

HEERSMA, Kalamazoo, Mich.

THE VASCULAR COMPLICATIONS OF CERVICAL RIBS AND FIRST THORACIC RIB ABNORMALITIES. KENNETH C. EDEN, Brit. J. Surg. **27**:117 (July) 1939.

Many who have written on cervical ribs have neglected to discuss the vascular anomalies associated with this condition, but Eden has reported on these in detail. In the majority of cases of vascular involvement pain is sooner or later experienced in the arm. It differs markedly from the pain in cases of nerve involvement, which is lancinating and shoots down the arm into the fingers. It is influenced considerably by posture, being provoked by carrying heavy articles in the hand or by relax-

ing the shoulders in an armchair or bed. In cases of vascular disturbance there is a characteristically cramplike pain in the muscles of the forearms, which is sometimes absent during rest but which comes on rapidly during use of the arm. When the muscles are tender the pain may take some minutes to wear off after vigorous exercise. In the latter case the pain is not of neuralgic origin but is due to muscular ischemia. The vascular changes in the arm are caused by the cervical rib or its counterpart and by the damage to the subclavian artery with thrombus formation.

In the presence of compression of the subclavian artery from a cervical rib or its counterpart, the simplest procedure is removal of the cervical rib.

STUCK, Denver. [ARCH. NEUROL. & PSYCHIAT.]

OSTEOPETROSIS (ALBERS-SCHÖNBERG DISEASE) IN AN INFANT OF TWO YEARS. REGINALD LIGHTWOOD and E. ROHAN WILLIAMS, Proc. Roy. Soc. Med. **33**:629 (Aug.) 1940.

A boy showed symptoms of anemia from the age of about 3 months. At the age of 6 months he weighed 10 pounds (4.1 Kg.), was small and backward and showed marked hypotonia and skeletal changes, presumed at the time to be rachitic. Examination of his blood at this time showed: red cells, 2,787,500 per cubic millimeter; hemoglobin content, 58 per cent; color index, 1.0; white cells, 13,500 per cubic millimeter, and reticulocytes, 15 to 20 per cent. The anemia resisted treatment. Recent examination (at the age of 2 years) showed a dwarfed, anemic and apparently mentally defective child; the skull was enlarged and markedly dolichocephalic; primary atrophy of the optic nerve and enlargement of the liver and spleen were also noted. Roentgen examination showed striking generalized changes in the skeleton, due to osteopetrosis. They consisted chiefly of: (*a*) marked clubbing at the ends of the shafts of the long bones; (*b*) vertical fissuring in the metaphysial zones, described by Brailsford; (*c*) sclerosis at the base of the skull, with marked thickening of the frontal bone and clubbing of the posterior clinoid process, and (*d*) dense sclerosis in the ribs and the vertebral bodies.

The degree of osteopetrosis was most unusual for the age of the patient, and with such bone lesions one would anticipate a rapidly progressive and severe anemia. Roentgen examination of the sister of the patient showed no abnormal changes.

WILLIAMSON, New Orleans.

PERTHES' DISEASE. STEPHAN ELBERS, München. med. Wchnschr. **87**:535 (May 17) 1940.

The author discusses Perthes' disease and reports a case. Perthes described the condition as a subchondral focus of degeneration in the epiphysis and named it osteochondritis deformans juvenilis. It is caused by a disturbance in the development of the center of ossification in the growing femur and is often associated with some hereditary factors. Some authors believe the condition is basically due to congenital subluxation of the head of the femur.

Elbers reports the case of a boy whom he first saw at the age of 15 years. Two days before admission to the hospital the patient experienced a severe pain in the left hip. Treatment was conservative, consisting of traction, abduction and the administration of calcium, ascorbic acid and a vitamin D preparation. After nine weeks of treatment the child was taken home by the parents against medical advice. After three years the patient was reexamined. He did heavy manual labor and felt uncomfortable only when the weather changed. Roentgenograms revealed coxa vara. Elbers emphasizes that it is not sufficient to treat a patient with Perthes' disease and then discharge him without further observation. The patient should be treated for at least three months and examined monthly for a year after discharge.

BRAHDY, Mount Vernon, N. Y.

Skin Diseases; Allergy

ECZEMA OF INFANCY AND EARLY CHILDHOOD: ITS PEDIATRIC MANAGEMENT. CRAWFORD BOST, California & West. Med. **54**:24 (Jan.) 1941.

Bost differentiates seborrheic dermatitis from atopic dermatitis, the disorder commonly called infantile eczema. Seborrheic dermatitis starts on the scalp, the cheeks or the forehead or as circumscribed patches on the trunk or the extremities. The lesion consists of papules which become covered with greasy scales; itching is slight or absent, and there is usually no family history of allergy. Consumption of a low fat, high protein diet or an evaporated milk formula with the substitution of a cod liver oil concentrate for the oil itself will usually benefit infants with this disease. In cases of atopic dermatitis papules, vesicles, scales, erythema, weeping areas and crusting may all be present. Itching is severe, and a family history of allergy is usually obtained. Therapy should consist of proper local treatment (which may be all that is necessary in cases of the mild form of the disease), dietary measures and environmental control. Inhalant substances are often of major importance as causative agents; cutaneous tests with them should be carried out. Keeping the child in a "dust controlled" environment for the greater part of the time is advised.

DAVIS, San Francisco.

THE VALUE OF ELIMINATION DIETS IN THE TREATMENT OF INFANTILE ECZEMA. ARTHUR R. BIRT, Canad. M. A. J. **43**:520 (Dec.) 1940.

Since 1930, 198 patients with infantile eczema have been treated at the Children's Hospital, of Winnipeg, Manitoba, Canada. Of these patients 63 per cent were boys. In two thirds of the cases the disease started before the sixth month and in four fifths before the end of the first year of life. Forty-two per cent of the infants still had eczema at 1 year, 28 per cent at 18 months and 25 per cent at 2 years of age.

Cutaneous tests were not used routinely in these cases. It was felt that they would complicate the routine of diagnosis and, also, that results reported in the literature were too varied as to the value of such tests to warrant using them.

The taking of a careful history and the use of elimination diets were the mainstays of the diagnostic routine. The details of the diets used are given.

All patients treated with combined local and dietetic therapy were either improved or cured.

Fifty-four patients who had had infantile eczema five to ten years previously and who had been treated by local measures only were followed up. Twenty-five per cent of them had other evidence of atopy, and 25 per cent had contact dermatitis.

MOORE, Omaha.

HEMANGIOMAS OF THE SKIN. GRANT E. WARD and E. EUGENE COVINGTON, J. A. M. A. **114**:2069 (May 25) 1940.

The treatment of 127 hemangiomas over an eight year period gave the figures analyzed in this article. The earlier the age at which treatment begins the better the results. Other factors influencing results include the type of tissue of origin, the location and depth and the occurrence of infection or other conditions which decrease radiosensitivity. The methods of treatment in order of preference (in each case the opinions of a roentgenologist and a surgeon should be sought) are radium therapy, electrosurgery, application of solid carbon dioxide, use of sclerosing solution, interstitial electrocoagulation and surgical excision. The technics, complications, residuals and method of evaluating results are described. Typical photographs illustrate the types of lesions and locations and results.

HEERSMA, Kalamazoo, Mich.

ORAL POLLEN THERAPY IN RAGWEED POLLINOSIS: A COOPERATIVE STUDY. SAMUEL M. FEINBERG, FRANCIS L. FORAN, MEYER R. LICHTENSTEIN, EMANUEL PADNOS, BEN J. RAPPAPORT, JOHN SHELDON and MICHAEL ZELLER, J. A. M. A. **115**:23 (July 6) 1940.

Three separate groups of patients sensitive to pollen were treated in a controlled study with oral administration of pollen extract. The general results were unfavorable as compared with the improvement obtained from parenteral desensitization. In the small number of children given pollen extract orally, especially in those who received large doses, some improvement occurred; the improvement was of sufficient magnitude to make one recognize that the procedure has possibilities. Untoward reactions were frequent but not severe; they were chiefly related to the gastrointestinal tract.

HEERSMA, Kalamazoo, Mich.

CHOLINESTERASE IN THE BLOOD OF ALLERGIC PATIENTS. ROLAND C. HAYES and GORDON A. ALLES, J. Allergy **12**:1 (Nov.) 1940.

The cholinesterase activity of the whole blood of allergic and of normal persons was studied. This was done on the assumption that if parasympathetic hyperexcitability is present in an allergic person it might be reflected in or caused by an alteration of the cholinesterase content of the blood, since the parasympathetic nerves are cholinergic.

The authors' conclusions read as follows:

"Titrations by a highly precise method of the activity of whole blood enzymes in splitting acetylcholine ion showed no difference between normal and allergic persons, even during attacks of asthma.

"The results confirm the reports of others in showing a relatively wide range of normal values and no sex or age differences."

HOYER, Cincinnati.

TIME REQUIRED FOR THE PRODUCTION OF HAY FEVER BY SPORES OF A NEWLY ENCOUNTERED FUNGUS, JOHNSON GRASS SMUT. E. W. PHILLIPS, J. Allergy **12**:24 (Nov.) 1940.

Johnson grass smut was first observed in Arizona in 1931 and by the author in 1933. The spores of the smut are in the air for eight months of the year, from April to frost in December.

Extracts of the smut used intradermally in testing patients suffering from hay fever elicited no positive reactions in 1935 or in subsequent years until 1938. In 1939, of 131 persons known to be sensitive to inhaled allergens who were tested with an extract of the smut, 34 had a positive reaction to it. All of the positive reactors had lived for at least five years in regions where the smut was prevalent. Fifteen of the positive reactors were relieved from recurrences of hay fever or asthma when smut extract was added to their otherwise adequate treatment.

So far, the smut has been a subsidiary, rather than a primary, cause of inhalant allergy.

HOYER, Cincinnati.

FOOD SENSITIVITY AS A FACTOR IN THE ETIOLOGY OF ACNE VULGARIS. FRANK E. CORMIA, J. Allergy **12**:34 (Nov.) 1940.

The author feels that the ingestion of certain foods frequently makes worse a type of acne that affects skin which is delicate rather than coarse and which is characterized by a moderate, though variable, degree of seborrhea.

The use of elimination diets and the removal of reactive foods result in clinical improvement in 50 to 70 per cent of the cases in which food sensitivity is demonstrated.

The foods most commonly found to cause flare-ups were chocolate, tomatoes, nuts, spinach and wheat.

Scratch and intracutaneous tests were of little aid in discovering which foods caused clinical exacerbations.

HOYER, Cincinnati.

THE ASCORBIC ACID CONCENTRATION OF INFLAMMATORY LESIONS OF THE SKIN. CALVIN C. TORRANCE, J. Infect. Dis. **67**:53 (July-Aug.) 1940.

"The ascorbic acid concentration of the dermal lesions induced in guinea pigs, rabbits, and rats by diphtheria toxin was found to be significantly lower than that of the corresponding uninjected areas on the opposite side of the body. Similar changes occurred in the vitamin C concentration of the dermal lesions induced by heat. No such changes were found following the injection of toxin into the skin of rats in which the dose given induced no inflammatory reaction. It appears from these experiments that the observed changes in the ascorbic-acid concentration are associated with the development of the inflammatory lesion and are not directly influenced by the presence of the toxin. It is suggested that the total amount of ascorbic acid in a local lesion may affect capillary permeability and thus the edema."

TOOMEY, Cleveland.

HISTAMINE THERAPY IN ALLERGY. LEON D. PORCH, J. Lab. & Clin. Med. **26**:499 (Dec.) 1940.

The author discusses the treatment of certain allergic conditions with histamine dihydrochloride. Among the conditions which were treated with improvement were urticaria, infantile eczema and cutaneous lesions of older patients. A small series of patients with gastroduodenal ulcers also showed improvement with this type of therapy.

GARD, Galveston, Texas.

RECURRENT CUTANEOUS ABSCESSES AND THE USE OF MATERNAL BLOOD–VACCINE THERAPY. A. C. DE FREITAS MOURÃO, Bol. Inst. de puericult. **2**:111, 1940.

The author presents clinical observations in the case of a 9 month old nursing infant with generalized recurrent cutaneous abscesses, in which excellent results were obtained within a few days by intramuscular administration of pyogenic bacillus vaccine and maternal blood.

He discusses this method of therapy and draws attention to its simple technic and effective results. He believes that the injection (intramuscular) of maternal blood or of the patient's own blood (autohemotherapy) brings about a nonspecific stimulus to the production of antibodies which increases the organic defenses of the infant and shortens the duration of the disease.

SOTO, Habana, Cuba.

ALLERGIC FLORA OF THE VALLEY OF MEXICO. MARIO SALAZAR MALLEN and PIERRE LYOMRET, Prensa méd. mex. **9**:163 (Dec. 15) 1940.

The authors for over a year, from the spring of 1938 to the summer 1939, have studied the flora during weekly excursions within the cities and their environs. They have made a fundamental classification of the allergens of trees, grasses and vegetables.

It is interesting that pines are abundant in the city itself and, especially, in the adjacent mountains. Pines are great producers of pollen from the end of February to the middle of May.

The authors have evidently worked hard on their studies and have classified all the trees, grasses and vegetables, giving the dates of pollenation of each. Since many of the trees and vegetables are unknown here, details are omitted.

GIFFEN, Toledo, Ohio.

POLLENS IN THE ATMOSPHERE OF MEXICO CITY. MARIO SALAZAR MALLEN, Prensa med. mex. **9**:166 (Sept. 15) 1940.

The article is accompanied by a chart showing the seasonal incidence of the pollens of ambrosia, cedar, aile (pine) and oak and good drawings of them. The pollens of grasses are spherical granules 34 to 35 microns in diameter, with

germinal openings measuring 3.5 microns; the central pollen is granular. The grasses have a profuse pollen which is light in weight and is present in the air from the middle of February to the rainy season in June.

The pollen of cedar measures from 25 to 30 microns in diameter; its germinal center is narrow and sparsely provided with granules on the surface. The granules are easily recognized, because they are egg shaped, have in the center an irregular or star-shaped spot and are the green of methyl. The first granules were observed early in September; they were noted constantly after that, but they do not number more than 5 per cubic centimeter per twenty-four hours until the middle of September, when a marked increase was noted to 30 to 45 granules for the same surface and time; the number decreased in September to the previous level, but a less pronounced rise occurred during the first ten days of January, followed by a new diminution and increase, so that the number of 10 granules per day was exceeded, and the curve then decreased progressively to zero at the end of May.

In the months of June, July and August, he could exceptionally identify a granule on his slides. Strictly speaking, the pollen of cedar is present from September until the beginning of May, but allergic disturbances caused by it mostly occur from the middle of December to the first of February.

GIFFEN, Toledo, Ohio.

TREATMENT OF IMPETIGO WITH ADHESIVE TAPE. F. SCHULER, Kinderärztl. Praxis **11**:354 (Nov.) 1940.

The simple treatment described is recommended. On the first day the impetiginous lesion is covered with adhesive tape. If the tape does not stick well, it should be warmed slightly. The crusts are removed with the tape on the second day. The slightly bleeding lesion is cleaned with gauze and benzine and again covered with adhesive tape. Such application and removal of the tape is repeated until the impetigo is healed. The duration of the treatment is usually from four to six days.

HEYMANN, Cleveland.

Miscellaneous

ASCORBIC ACID IN THE TREATMENT OF CHRONIC LEAD POISONING. ARTHUR M. DANNENBERG, ARNOLD H. WIDERMAN and PAUL S. FRIEDMAN, J. A. M. A. **114**:1439 (April 13) 1940.

A 27 month old boy with typical lead poisoning was treated with large doses of ascorbic acid, with apparent progress of the symptoms.

Changing to the usual administration of calcium and phosphorus brought rapid improvement.

HEERSMA, Kalamazoo, Mich.

CLINICAL TOXICITY OF SULFANILAMIDE AND SULFAPYRIDINE. W. H. BROWN, W. B. THORNTON and J. STUART WILSON, J. A. M. A. **114**:1605 (April 27) 1940.

In comparing the toxic effects of sulfanilamide and of sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine) the authors studied the records of 200 patients who were receiving large doses of the drugs, half of whom got one and half the other compound. They found that the troublesome vomiting which occurred, especially with the use of sulfapyridine, could be lessened by administering the drugs in mucilage of tragacanth and by giving nicotinic acid.

The serious toxic reactions were twice as frequent with sulfapyridine, principally because of the high incidence of complications referable to the urinary tract. The hematuria and anuria which may occur when sulfapyridine is administered are due to precipitation of the acetylated form of the drug. This difficulty can be avoided by increasing the urinary output.

Acute hemolytic anemia was more common with sulfanilamide therapy, while granulocytopenia occurred only with the use of sulfapyridine.

The length of treatment and the concentration of the drug in the blood were important factors.

HEERSMA, Kalamazoo, Mich.

SOME RESPONSES OF THE CHILD TO EXERCISE. FREDERIC W. SCHLUTZ, MINERVA MORSE and JOHN L. GEDGOUD, J. Pediat. **16**:729 (June) 1940.

"The effects of exercise have been studied intensively in twelve children from 11 to 13 years of age. The study has included determinations of the changes in heart rate and systolic and diastolic pressures, resulting from both moderate and maximal work on the bicycle ergometer, and determinations of the changes in many of the blood components under the two conditions of work. An attempt has also been made to relate these changes to the nutritive status and to the physical capacity of the child.

". . . Pulse rate and systolic pressure increased with exercise, but as work was changed from a moderate to a maximal character little further increase occurred as a rule. Diastolic pressure showed great variability of response under either condition of work, decreasing in the majority of children during moderate exercise, but showing an increased tendency to rise during maximal exercise.

"Hemoglobin, red cell volume, and serum protein increased with both moderate and maximal exercise. . . .

"The sodium and chloride concentration of the serum showed little change. . . .

"Serum phosphate increased during both moderate and maximal exercise. . . . Blood sugar . . . increased slightly in the majority of persons [during exercise].

"Serum lactate increased, on the average, by 3.5 meq. during moderate exercise, and by 7.8 meq. during maximal exercise. Serum bicarbonate, corrected to initial p_H, showed a corresponding, but slightly greater, fall. The p_H . . . decreased on the average, by 0.09 during maximal work.

". . . Superior physical capacity is indicated in the child, as well as in the adult, by the lack of a significant rise in serum lactic acid and a corresponding fall in bicarbonate when a fixed moderate task is performed."

RAUH, Cincinnati.

METHEMOGLOBINEMIA FOLLOWING SULFANILAMIDE AND SULFAPYRIDINE THERAPY IN INFANTS AND CHILDREN. BENJAMIN W. CAREY and JAMES L. WILSON, J. Pediat. **17**:38 (July) 1940.

"Data from infants and children have been presented in an attempt to correlate the dose of sulfanilamide and sulfapyridine [2-(paraaminobenzenesulfonamido)-pyridine] and the blood level, the relation of the methemoglobin level of the blood and the blood concentration of sulfanilamide and sulfapyridine, and the relation of the percentage of the total hemoglobin changed to methemoglobin at different blood levels of the drugs.

"There is apparently little relation between the dose of these drugs and the blood levels of the 'free' amounts of the substances. . . .

"There seemed to be no definite relation between increasing amounts of methemoglobin and increasing blood concentrations of 'free' sulfanilamide and sulfapyridine. . . .

"In comparing the percentage of the total hemoglobin changed to methemoglobin at different blood levels of sulfanilamide and sulfapyridine, the tendency toward increasing the percentage of the methemoglobin as the blood levels increased was only slight."

RAUH, Cincinnati.

FATAL AGRANULOCYTOSIS AFTER SULFAPYRIDINE (M & B 693) THERAPY. W. K. ANDERSON, S. HOROWITZ and T. W. PALMER, Glasgow M. J. **16**:172 (Nov.) 1940.

A 32 year old married woman was admitted to the hospital with an infection of the throat and pyuria. She had a mild degree of anemia. Pneumonia developed, and she received 75 Gm. of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) over a period of one month. The pneumonia improved, but the red and white cell counts of her blood dropped. There was slight improvement; then a second infection of the throat occurred. She had a large hemorrhage. Sternal puncture showed immature granular forms, such as myelocytes and myeloblasts, with few mature forms. An epinephrine test of the bone marrow showed a defective marrow response. Her course continued downhill, and she died.

SNELLING, Toronto, Canada.

BACTERIOLOGIC EXAMINATIONS AS DECISIVE DIAGNOSTIC AIDS IN DISEASES OF CHILDHOOD. H. KLEINSCHMIDT, Jahrb. f. Kinderh. **149**:267 (Aug.) 1937.

The various bacteriologic examinations, including cultures of the blood and urine, examinations of the spinal fluid, cultures of material from the nose, throat and ear and cultures of the pleural fluid and stools are discussed. Smears of material from the eye, animal inoculations and the advantages of the cough plate method for the diagnosis of whooping cough are also considered carefully. The special advantage of accurate bacteriologic diagnosis since the advent of modern chemotherapy is stressed.

LANDAU, Hannibal, Mo.

DIGITALIS POISONING IN CHILDHOOD. T. VARGA and K. GREINER, Orvosi hetil. **84**:188 (April 13) 1940.

Through the carelessness of her parents, a healthy 3 year old girl weighing 12 Kg. took 2 Gm. of digitalis and 4 Gm. of theobromine at one time; the medicine had been prescribed for her father. The girl vomited frequently, and the next day she was brought to a physician, who washed out her stomach and sent her to the clinic, where severe poisoning developed. The girl continued to vomit frequently, the pulse was quick and arrhythmic and the blood pressure rose. Erythema appeared on the face and chest, and the legs became rigid. Anuria developed and lasted for forty-eight hours. Besides lesions of the heart muscle, the electrocardiographic examination showed extrasystoles and atrioventricular block. The child recovered in three weeks. The reason for this fortunate outcome was probably that theobromine was taken simultaneously with the digitalis. While the digitalis caused stricture of the coronary arteries, elevation of the blood pressure and anuria, its effect was counterbalanced by that of theobromine, which enlarges the coronary arteries, lowers the blood pressure and stimulates diuresis.

GÖTTCHE, Budapest, Hungary.

RESULTS OF SULFANILAMIDE THERAPY. J. MUNK, Maandschr. v. kindergeneesk. **10**:26 (Oct.) 1940.

The writer discusses the remarkable activity of sulfapyridine (2-[paraaminosulfonamido]-pyridine) and its failure to effect a cure in some interesting cases of pneumococcic infections. In 1 case of pneumococcic meningitis with nephritis complete recovery was obtained by means of this drug.

VAN CREVELD, Amsterdam, Netherlands.

Society Transactions

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

LIONEL M. LINDSAY, M.D., *President*

ELIZABETH CHANT ROBERTSON, M.D., *Secretary-Treasurer*

Eighteenth Annual Meeting, Brockville, Ontario, Canada, June 14, 1941

First Session

Saturday Morning

Presidential Address. DR. LIONEL M. LINDSAY, Montreal.

Variations in the Size of the Heart in Rheumatic Fever. DR. J. D. KEITH, Toronto.

A study based on successive roentgenograms of the heart during an attack of rheumatic fever is described. One hundred children were investigated. All but 4 had signs of rheumatic disease of the myocardium, the endocardium or the pericardium, and in these 4 the signs were doubtful.

It was found that dramatic dilatation of the heart did not occur but a moderate increase in size sometimes took place over a few weeks. The return to normal was never rapid and was accomplished as a gradual process over several months. Of the 100 hearts examined, 33 became larger, 18 remained unchanged and 49 became smaller. A rapid change in the heart shadow was found only in the cases of patients with pericarditis. The patients who improved usually showed a decrease of more than 20 square centimeters in the size of the heart within one month.

Various points of interest may be illustrated by roentgenograms. The following observations have been made: 1. A rheumatic heart may become smaller than normal with continued rest in bed. 2. The heart of any child who has prolonged rest in bed will be smaller than normal. 3. The tendency of the heart muscle to revert toward normal is greater than that of the valve. This is shown by the fact that murmurs persist and become louder while the heart is getting smaller. 4. A roentgenogram will frequently show obvious changes in size that are not evident on clinical examination. 5. Tachycardia in itself does not produce enlargement of the heart unless it is paroxysmal and the heart rate is well over 200 beats a minute. 6. Dramatic dilatation of the heart has not been shown to occur in an attack of rheumatic fever. 7. Marked change in the heart shadow has been shown to occur only in the presence of pericarditis.

DISCUSSION

DR. EDWARD MORGAN, Toronto: Is the decrease in the size of the heart in the cases of pericarditis due to absorption of the pericardial fluid or to a decrease in the size of the heart itself?

DR. J. D. KEITH, Toronto: Undoubtedly the decrease in size is due to the absorption of the pericardial fluid.

Tuberculosis with Multiple Cystic Lesions of the Bones. Dr. A. K. Geddes, Montreal.

Two cases of a rare form of tuberculous involvement of the bones are presented. Only 13 cases are found in the pediatric literature. Case 2, in which biopsies, isolation of the organism and autopsy were carried out, is the most completely studied case on record.

Case 1.—A 7 year old girl with no known exposure to tuberculosis began to have disability of the right arm at the age of 5 years. Two years later the right shoulder was ankylosed. Multiple cystic lesions of the humerus and the scapula were seen on roentgen examination, and calcified glands were demonstrated in the lung. The reaction to tuberculin was strongly positive.

Case 2.—Examination of a 13 month old girl showed a lesion of the second metacarpal bone, a large cystic lesion in the upper portion of the left tibia, massive pulmonary consolidation, a chronic hypertrophic lesion of the skin of the dorsum of the left foot, a strongly positive reaction to tuberculin and the presence of tubercle bacilli in washings of the stomach.

Tubercle bacilli were isolated from biopsy material taken from the left tibia. Histologic examination of the cutaneous lesion showed tuberculosis. The child died six months later of bacteremia due to Staphylococcus pyogenes aureus. The right lung showed an area of healing primary tuberculosis, drained by a lymph node which was caseous. The results of histologic studies of the lesions in the bone, the skin and the lung are presented.

A Case of Generalized Torulosis in Which Autopsy Was Performed. Dr. Jessie Boyd Scriver, Dr. Eleanor R. Mackenzie (by invitation) and Dr. N. W. McLellan (by invitation), Montreal.

Generalized torulosis is a fatal disease caused by invasion of the host by Torula histolytica, a yeastlike organism which reproduces by budding without the formation of myceliums or spores. The case reported is that of a 3 year old French-Canadian child who was admitted to the hospital with a history of jaundice, vomiting, red urine, white stools, cough and cold of one week's duration. On examination the outstanding feature was a stony-hard abdominal mass about 2 inches (5 cm.) in width which extended from the left flank medially past the midline. Laparotomy revealed this to consist of enlarged hard isolated mesenteric glands, one of which showed an extensive granulomatous lesion replacing the normal lymph node tissue. Countless yeastlike organisms were present throughout the node.

One week later an enlarged cervical gland was removed, and examination revealed a similar lesion; from this gland T. histolytica was cultured. The same organism was subsequently recovered from the blood stream on two occasions and from all the organs at autopsy. The child lived for eleven weeks after admission to the hospital. So far as is known this patient is the youngest in any case of generalized torulosis on record. The disease involved the liver, spleen, pancreas, lungs, kidneys, lymph nodes, brain and meninges, as was proved by histologic examinations and by cultures made during life and post mortem.

An interesting feature is the primary abdominal infection, which apparently arose via the gastrointestinal tract. A definite predilection of the organism for lymphatic tissues was demonstrated. The brain and the lungs were apparently involved only in the late stage of the disease.

DISCUSSION

Dr. H. P. Wright, Montreal: What dose of potassium iodide did you use, and how long did you give it?

Dr. Jessie Boyd Scriver, Montreal: Reports in the literature state that potassium iodide has been useful for clearing up the cutaneous lesions in this

disease, but it has never proved useful for the treatment of visceral or meningeal lesions caused by torulosis. In this case we gave 5 grains (0.32 Gm.) of potassium iodide three times daily.

DR. H. P. WRIGHT, Montreal: I asked this question because potassium iodide is useful in the treatment of actinomycosis, but large doses are needed.

DR. JESSIE BOYD SCRIVER, Montreal: In the cases reported in the literature large doses of potassium iodide were given.

DR. EDWARD MORGAN, Toronto: I noticed that you report that the cervical lymph nodes were enlarged. Were the tonsils enlarged? Could the point of infection have been the tonsils?

DR. JESSIE BOYD SCRIVER, Montreal: The tonsils were enlarged but not markedly. The lymph nodes were enlarged before the tonsils were involved. The point of infection was apparently the gastrointestinal tract.

DR. ALAN ROSS, Montreal: I should like to ask whether this severe infection was caused by an unusually pathogenic strain of the organism or was due to a high degree of susceptibility of the host.

DR. ELEANOR R. MACKENZIE, Montreal: I think that it was probably due to the high susceptibility of the host.

Pathologic Changes in Mumps Meningoencephalitis. DR. W. L. DONOHUE (by invitation), Toronto.

Reports of cases of mumps encephalitis in which microscopic study of the central nervous system has been carried out are few. The pathologic changes mentioned in the few reports are varied and from these descriptions it is difficult to determine the characteristic histologic changes in the disease.

Microscopic examination of the central nervous system in a fatal case of mumps encephalitis showed perivascular demyelination with attendant reaction on the part of the glial and mesodermal tissues. These changes are identical with those of the so-called postinfection encephalitides which follow such diseases as vaccinia and measles. These observations are in agreement with those in the typical cases of mumps encephalitis reported in the literature.

DISCUSSION

DR. LIONEL M. LINDSAY, Montreal: There has been an epidemic of mumps in Montreal this winter. I have not heard of any case terminating fatally, but no doubt there were some deaths. Perhaps Dr. Cushing knows.

DR. H. B. CUSHING, Montreal: I did not hear of any one dying of mumps in Montreal. I did hear of half a dozen patients with mumps meningoencephalitis, all of whom recovered.

DR. A. P. HART, Toronto: This year I saw a boy who came home from school complaining that he could not use his legs. I though he had slight stiffness in the neck, but it was not definite. I examined him carefully for any signs of tenderness about the parotid and cervical glands, but there were none. The next day he seemed better, according to the parents. The third day they called me in, and I found that there was definite stiffness of the neck, although he was mentally alert. I sent him into the hospital for lumbar puncture; examination of the cerebrospinal fluid showed an increased cell count. There still were no signs of parotitis or tenderness, but the next morning both parotid glands were enlarged. Apparently one can have mumps encephalitis or signs of involvement of the nervous system three or four days before mumps appears. I have the impression that in the various epidemics of mumps there has been a great deal of difference in the number of cases of mumps encephalitis which have occurred. Twelve or fifteen years ago during an epidemic of mumps I saw at least 12 patients with encephalitis, and I have seen practically none since then.

DR. S. GRAHAM ROSS, Montreal: I saw a patient somewhat similar to Dr. Hart's; the child had encephalitis first, and after three or four days mumps developed.

DR. ALTON GOLDBLOOM, Montreal: I think it is important to point out in this connection that one may encounter cases of encephalitis due to the mumps virus in which there is no involvement of the parotids or the other salivary glands. Dr. Cushing and I were both associated with such a case some years ago. Just at the end of the epidemic of poliomyelitis a child was admitted to Children's Memorial Hospital with a condition which I diagnosed as poliomyelitis without paralysis. This diagnosis was supported fully by Dr. Cushing. The child remained ill for about three weeks, during which time his temperature fell slowly. The first suggestion that we were dealing with mumps meningoencephalitis without other signs was the fact that mumps developed in the nurse who attended the child eighteen days after he was admitted. Mumps also developed in the mother and another child at home on the same day. Otherwise we could not possibly have known that the disease was mumps encephalitis. Apparently mumps meningoencephalitis can occur not only before or after the parotitis but without it.

DR. I. H. ERB, Toronto: I think that a permanent record should be made of these 3 cases, for they help to support the view that encephalitis may be caused by the mumps virus.

Treatment of Meningococcic Infections. DR. H. B. CUSHING and DR. DAVID KLEIN (by invitation), Montreal.

There has been a great increase in the prevalence of meningococcic infections during 1940 and 1941, presumably because of war conditions; in most parts of Canada there have been about ten times the previous number of cases.

With former treatment, employing rest and sedation, the mortality was 50 per cent. With the use of Flexner's serum this was reduced to 25 or 30 per cent, but by the administration in the past three years of sulfanilamide and its derivatives the mortality has been reduced to 5 or 6 per cent. Most recent writers agree on the following principles:

1. All patients should be strictly isolated in separate wards to eliminate the problem of carriers.

2. Since the meningococcus is unusually susceptible to the action of sulfanilamide and its derivatives, all patients should be immediately placed under a regimen employing full doses of one of these drugs.

3. The dose for the first two days should be at least 2 grains per pound (0.13 Gm. per 0.5 Kg.) per day for small children and 1½ grains (0.9 Gm.) per pound for adults, the initial dose (given intravenously if the need is urgent) being half the daily dose.

4. After the first two days the dose can be rapidly reduced, but a certain amount of the drug should be given for two to ten days to avoid relapses and complications.

5. The use of specific serum in addition is unnecessary, and its intrathecal administration in particular should be avoided.

6. Lumbar puncture should be performed as seldom as possible, and in the average case it should be avoided altogether.

7. The level of the drug in the blood should be 3 or 4 mg. per hundred cubic centimeters; the level in the cerebrospinal fluid seems to be entirely unimportant.

DISCUSSION

DR. LIONEL M. LINDSAY, Montreal: I think that the authors have expressed the view of Montreal physicians on this subject.

DR. EDWARD MORGAN, Toronto: I should like to ask Dr. Cushing a question, which perhaps is not important except from the standpoint of immunity: Has he ever observed a second attack of meningococcic meningitis?

DR. H. B. CUSHING, Montreal: I have observed numerous relapses of the disease but never a second attack occurring some years after the first.

The B Group of Vitamins in Relation to National Health. DR. FREDERICK F. TISDALL, DR. S. H. JACKSON (by invitation) and DR. T. G. H. DRAKE, Toronto.

Nutritional surveys have shown that the Canadian people as a whole are not receiving the amount of vitamin B_1 necessary for optimum mental and physical efficiency. McHenry has pointed out that the distribution in foods of the other members of the vitamin B complex parallels to a degree that of vitamin B_1. The adequacy of the amount of vitamin B complex in the Canadian diet as a whole is open to question.

Canadian agriculture produces foods which are rich in the various members of the vitamin B complex, particularly wheat and milk. At least one of the new Canadian rust-resisting wheats, which will soon constitute a large portion of the commercial wheat grown in the West, is very rich in vitamin B_1. Unfortunately, because of the process of milling now used white flour retains only about one sixth of the original vitamin B_1 content of the wheat, a small percentage of the original concentrations of the other members of the vitamin B complex and only one seventh of the original iron content.

The retention of these valuable food elements now lost for human consumption is engaging the attention of members of the department of agriculture and various millers throughout Canada. The per capita consumption of Canadian flour has steadily decreased over the past forty years. Anything which can be done to increase the use of Canadian wheat and flour through increasing its nutritional value is obviously of the greatest importance to Canada, not only from the standpoint of improving the health of the nation but from the agricultural and economic standpoints. At the present time the Canadian government, through the Canadian wheat pool, is the (proud?) owner of $350,000,000 worth of wheat.

Under the leadership of Dr. L. H. Newman, cerealist of the Dominion of Canada, white flour has been produced experimentally which retains from two thirds to three fourths of the vitamin B_1 originally present in the wheat and an appreciable amount of the other members of the vitamin B complex. It is hoped that white flour may be produced commercially in Canadian mills which will contain a much greater proportion of vitamin B complex than that contained in the baker's white flour now commonly used. It is hoped that this may be accomplished with no increase in milling cost and with the use of the present milling machinery. White bread made from this flour and 4 per cent skimmed milk solids would supply appreciable amounts of the various members of the vitamin B complex. Studies of the public reaction to bread made from this flour indicate that it is acceptable to over 90 per cent of the people as white bread. The use of this flour by the Canadian people in place of the present white flour would supply for nothing in the course of one year many millions of dollars worth of vitamin B complex at drugstore prices. Probably no one dietary change would be of greater importance in improving the health and efficiency of the nation than the substitution of this white flour, in which the vitamins are retained, for that now being used in Canada.

DISCUSSION

DR. H. P. WRIGHT, Montreal: How many members of the vitamin B complex are contained in yeast?

DR. FREDERICK F. TISDALL, Toronto: The amounts of the members of the vitamin B complex vary in the different varieties of yeast. Ordinary yeast does

not contain a tremendous amount of vitamin B_1, but some special yeasts do. Milk is high in riboflavin (vitamin B_2) but low in vitamin B_1.

Dr. S. J. Usher, Montreal: How similar is the question of the lack of vitamin D in modern foods to the lack of vitamin B complex?

Dr. Frederick F. Tisdall, Toronto: There is no connection with the question of vitamin D. There are no foods which contain vitamin D in appreciable amounts. It must be added to the diet. It is not a comparable problem. I suppose man was meant to get vitamin D from sunshine. With vitamin B complex it is a question of retaining the vitamins already present in the wheat.

Dr. H. P. Wright, Montreal: The vitamin content of various fodders differs. Does such variation affect the vitamin content of the milk?

Dr. Frederick F. Tisdall, Toronto: Yes; many studies have been made on this point. The content of riboflavin, which is produced by bacterial action, does not vary with the food the cows eat, but that of the other vitamins does. Thirty imperial ounces (852 cc.) of milk per day provides nearly all the riboflavin that is needed. The nicotinic acid content of milk is also high.

Dr. S. Graham Ross, Montreal: Dr. Tisdall has made a rather general statement to the effect that the actions of the members of the vitamin B complex are interrelated. I wish he would elaborate briefly on this. I understand that there are deficiency states caused by combined deficiencies of members of the vitamin B complex. Does a deficiency of one member of the vitamin B complex interfere with the activity of the other members of this group?

Dr. Frederick F. Tisdall, Toronto: A considerable amount of clinical work is being done in the southern part of the United States, where diseases obviously caused by deficiencies of these factors occur. Spies, Sydenstricker and other workers have stated that they have never observed a deficiency of a single member of the vitamin B complex; the deficiency is always multiple. In the laboratory it has been shown that vitamin B_1 is needed for the normal production of fat from carbohydrate and that vitamin B_6 is needed for the metabolism of protein. Also, the actions of pantothenic acid and riboflavin are interrelated. The latest work concerns the factor known as inositol, which fits in definitely with the other members of the vitamin B complex. The members of the vitamin B complex are absolutely essential for the internal metabolism of practically every cell in the body.

Dr. C. E. Snelling, Toronto: Some of the drug companies have claimed that by greatly stepping up the intake of one of the factors of the vitamin B complex one may precipitate a deficiency of one of the other factors. Is this the case?

Dr. Frederick F. Tisdall, Toronto: My associates and I have done no work ourselves on this question, but that statement has been made by other workers in the clinical field. The situation is perhaps comparable to that which occurs in rickets; that is, if the baby is not growing he does not show rickets; if one makes him grow by adding other food factors which are lacking, the rickets appears.

Second Session

Saturday Afternoon

Serious Injury to the Rectum from Improperly Administered Enemas.

Dr. Alton Goldbloom and Dr. H. C. Ballon (by invitation), Montreal.

A case is reported in which an enema given with a hard nozzle to a 7 year old child resulted in an injury to the rectum, manifested by pain, bleeding, midline abdominal mass and shock within twelve hours of the administration. Free blood was found in the peritoneal cavity at operation, and the serosa of the rectum was torn in several places. The child recovered after a stormy convalescence.

A review of the literature reveals that such accidents are not at all rare. Peritonitis, necrosis and stenosis have all been reported. There were some deaths, and some of the patients who recovered had to have a permanent colostomy. It is

pointed out that the administration of an enema in unskilled hands is not without risk. It is suggested that enemas should always be given to children with soft rubber catheters.

Cystic Fibrosis of the Pancreas. Dr. F. W. Jeffrey, Ottawa, Ontario.

Data from 90 cases of cystic fibrosis of the pancreas are analyzed, of which 88 were collected from the literature and 2 are reported here. The pathologic changes in this condition consist essentially of cystlike dilatations of the pancreatic ducts and acini filled with concretions and surrounded by fibrous tissue. In all of the cases in which the patient died after the neonatal period there was also evidence of an associated chronic infection in both lungs.

Clinically, the cases can be divided into three definite groups, according to the age at which death occurred.

In the cases of group 1 the patient died in the neonatal period. Death in most cases was attributed to stenosis of the intestinal tract, and the associated cystic fibrosis of the pancreas was unexpectedly discovered at necropsy.

In the cases of group 2 the patient died during the interval between the neonatal period and the age of 6 months. This group was characterized by the patient's failure to gain weight, the rather voluminous and sometimes frequent stools and a persistent infection of the respiratory tract.

In the cases of group 3 the patient died after the sixth month of life. All of the symptoms present in the cases of group 2 and, in addition, the clinical manifestations of the celiac syndrome were observed.

In all of the cases of groups 2 and 3 the patient succumbed to a chronic infection of the respiratory tract.

Cystic Fibrosis of the Pancreas and Its Relation to Bronchiectasis. Dr. C. E. Snelling and Dr. I. H. Erb, Toronto.

Nineteen patients with cystic fibrosis of the pancreas have been observed by us during the past twenty years. Five were observed between 1923 and 1925 and 14 between 1937 and 1941. The symptoms were failure to gain weight or loss of weight, vomiting, loose and frequent stools, colic and abdominal distention. The symptoms referable to the respiratory tract were cough, wheezing, rapid breathing and cyanosis. Malnutrition was observed in all cases. All of the patients had physical signs of pulmonary involvement, such as bronchitis, collapse, consolidation, bronchopneumonia and bronchiectasis, and all died as a result of the pulmonary infection. Roentgenographic examination showed fibrosis, pulmonary collapse and signs of bronchiectasis. Staphylococcus aureus was the predominating organism in most cases. Bronchiectasis or abscess of the lung, metaplasia of the epithelium and fatty infiltration of the liver were found in association with the cystic fibrosis of the pancreas.

A discussion of etiologic aspects of the process is given, and the suggestion is made that the condition in the lungs was the result of vitamin A deficiency, possibly secondary to pancreatic change, or that the whole condition was the result of a vitamin A deficiency in the mother before the child was born.

DISCUSSION OF THE PAPERS BY DR. JEFFREY AND DRS. SNELLING AND ERB

Dr. Haddow Keith, Rochester, Minn.: May I ask how the children with this condition die? I have had 2 patients admitted to my service because of acute respiratory difficulty. They did not live very long. In the first case no diagnosis was made except bronchiectasis, which was revealed by bronchoscopic examination. In the second it was thought that the condition might be of this type, but a definite diagnosis was not made. Both patients seemed to drown in their own secretions.

DR. ALTON GOLDBLOOM, Montreal: I think it is interesting that both Dr. Snelling and Dr. Jeffrey have been able to follow their patients right through to autopsy. My associates and I have had a somewhat different experience in that our patient is now 7 years of age and doing well. We carried out investigations which proved that the child has cystic fibrosis of the pancreas. Her sister died at 18 months of age, having had diarrhea from birth and what was supposed to have been whooping cough for twelve months before her death. Death occurred in 1929, and, in view of the known familial tendency of this condition, I am sure that she had the same disease. Another sibling died at 3 days of age; the cause of death was not known. Our patient has had diarrhea from the age of 3 months; she also had "whooping cough" at about 6 months of age and has never stopped coughing since. She weighed about 34 pounds (15.4 Kg.) when we first saw her. She had clubbed fingers and mild cyanosis and had been treated for celiac disease. The diagnosis on admission to the hospital was cystic fibrosis of the pancreas. Total cholesterol of the blood measured 80 mg. per hundred cubic centimeters; free cholesterol, 30 mg.; vitamin A, 0.80 mg. (normal, 1.5 mg.), and carotene, 0.04 mg. (normal, 0.08 mg.). By administration of large amounts of vitamin A the level of vitamin A in her serum was raised to 1.35 mg. and that of carotene to 0.07 mg. per hundred cubic centimeters. Duodenal aspiration yielded a secretion which contained neither trypsin nor lipase. The child is doing fairly well under a regimen of large doses of vitamin A and a low fat diet similar to that used in the treatment of celiac disease. She has gained 3 pounds (1.3 Kg.) in a few weeks. She formerly coughed up about a pint (473 cc.) of thick yellow sputum daily. Now she has practically no sputum.

DR. J. H. EBBS, Toronto: It seems that the differentiation between this disease and true celiac disease has been rapidly clarified in the past three or four years. Some etiologic basis for celiac disease should be found fairly soon, and certainly more effective methods of treating it are becoming available. I should like to ask Dr. Erb whether he has any explanation for the fact that in spite of routine autopsies this disease was not brought to the attention of physicians until a few years ago.

DR. I. H. ERB, Toronto: I am sure that the disease must be more prevalent now than in former years, for I feel satisfied that the diagnosis in such cases was not missed in previous years.

DR. EDWARD MORGAN, Toronto: Dr. Andersen's third group included the cases of older children, 3 to 4 years of age, with bronchiectasis. My associates and I have seen a tremendous number of patients with bronchiectasis in the Hospital for Sick Children, but none of them has shown cystic fibrosis of the pancreas at autopsy.

DR. C. E. SNELLING, Toronto: In Dr. Andersen's third group of cases the diagnosis was celiac disease and bronchiectasis was found at autopsy.

DR. T. G. H. DRAKE, Toronto: Dr. Snelling, are not these cases an argument for giving both vitamin A and vitamin D rather than viosterol alone?

DR. C. E. SNELLING, Toronto: A number of my patients have entered the hospital almost moribund and drowned, so to speak, in their own secretions. They were acutely ill with pneumonia, and culture of material taken by suction from the nasopharynx revealed staphylococci. Cultures of material taken from the lungs at autopsy yielded the same organism. These patients died within a few hours after admission. In regard to Dr. Goldbloom's remarks, my associates and I have been unable to make a diagnosis of this disease before autopsy. We followed up 1 patient who had typical clinical evidence of the disease, but the diagnosis was not confirmed at autopsy. Concerning Dr. Drake's question about vitamins A and D, I do not think there is any question that both vitamins should be given.

Vitamin B_6 (Pyridoxine Hydrochloride) in the Treatment of Pseudohypertrophic Muscular Dystrophy in Children. DR. H. M. KEITH, Rochester, Minn.

Subsequent to the report in March 1940 by Antopol and Schotland that administration of vitamin B_6 caused great improvement in the condition of some patients with pseudohypertrophic muscular dystrophy, my associates and I treated 10 such patients over periods ranging from two to eight months. Pyridoxine hydrochloride was given intramuscularly to the amount of 100 to 300 mg. weekly. An attempt was made to estimate any increase or decrease in strength by means of weight lifting. Five of the patients were unable to stand or walk. The other 5 were able to get about without a great deal of difficulty. Some of the patients received a vitamin E concentrate in addition to the vitamin B_6. In spite of persistent treatment with vitamin B_6 for as long as eight months no definite improvement could be shown in the condition of any of the 10 patients.

Treatment of Muscular Dystrophies with Vitamins. DR. W. A. HAWKE, Toronto.

The first part of this report deals with the difficulty in assessing the results of therapy in cases of muscular dystrophy in childhood. Errors are frequently made through the suggestion of the patient or parent and through the difficulties of accurately assessing the muscular power of patients with this disease. These difficulties probably explain to some degree the divergent results reported for the treatment of this disease with various substances.

A report is given on the treatment with various vitamins of 7 children, 6 of whom had the pseudohypertrophic type of muscular dystrophy and the seventh a distal atrophic type. Two of the children had severe involvement, 3 moderate involvement and 2 slight involvement. The patients were examined at monthly intervals, and at the beginning and end of the treatment with each vitamin the power of each muscle group was as carefully assessed as possible and the results charted. The patients were first given moderate doses of thiamine hydrochloride and, in addition, small amounts of vitamin B complex. The results were then compared with those for a period in which distilled water and placebos were given by mouth. No difference was noted between the results for the two periods of treatment, and no improvement was observed. The children were next given vitamin B_6 in large doses, with no improvement. They were finally treated with moderate doses of synthetic alpha tocopherol and large doses of the natural tocopherols. Again no definite improvement was noted.

The conclusion was reached that vitamins B_1, B_6 and E were of no definite value in the treatment of the muscular dystrophies of childhood.

DISCUSSION OF THE PAPERS BY DR. KEITH AND DR. HAWKE

DR. G. A. CAMPBELL, Ottawa, Ontario: My experience corroborates that of Dr. Keith. Two years ago I had the opportunity of studying 3 boys in one family, aged respectively 10, 7 and 5 years, who had pseudohypertrophic muscular dystrophy. In each case the disease started at the age of 5 years. Three sisters are normal. The father died of tuberculosis. I treated these children with vitamin B_6 for one year. During that time the progress of the disease was measured daily by estimating the time that the children took to rise from a prone to a standing position and the time taken to walk around the ward. All of the measurements were made by the same nurse. While the children were under treatment there was no progress in the disease, but since treatment has been stopped deterioration has been rapid.

Influence of Antepartum Diet on the Infant. Dr. J. H. Ebbs and Dr. Frederick F. Tisdall, Toronto.

Studies have been made on the influence of good and poor antepartum diets on the health and the course during pregnancy of 400 women and their offspring. Ninety women with poor diets and low incomes were supplied with certain essential foods daily throughout the latter half of the antepartum period. The others ate their usual diets, which were good or poor as the case might be. The women were therefore divided into three groups: those with a supplemented good diet, those with a good diet and those with a poor diet. Clinical observations and laboratory investigations indicate that the antepartum diet has a striking influence on the health of the mother during pregnancy, labor and convalescence. The diet during pregnancy also markedly affects the health of the child during the first few months of life.

The incidence of miscarriage, premature delivery and stillbirth was much less among the women supplied with a supplemented diet. The ability of the mother to nurse her infant successfully and the condition and progress of the baby in the hospital were better in the groups who received the supplemented and the good diet. The average birth weight of the infants born to the women in the poor diet group was slightly higher than that of the babies born to those who received extra food. When examined at 6 months of age, the babies born of mothers who received a good or a supplemented diet weighed more, were in better general health and had had fewer illnesses during the first six months of life. There were more deaths from infections among the infants born to the women in the poor diet group.

Studies of the levels of phosphatase in the mother's blood indicate the value of vitamin D in pregnancy.

DISCUSSION

Dr. Frederick F. Tisdall, Toronto: This work of Dr. Ebbs is of great importance. Infant mortality figures have gone down year by year except that for the first month of life the mortality rate has shown little change. This work indicates that one method of attacking the problem is not through the pediatrician but through the obstetrician. The cost of giving the extra food to these patients worked out at $25 per patient for the four and one-half months. Of the 120 patients in the poor diet group, 14 lost their babies. If proper food had been supplied to all the women in this group, these 14 deaths might have been prevented, at a cost of $214 per death. Three weeks ago Dr. Ebbs was invited to a conference in Washington, D. C., called by the President of the United States, on the relation of nutrition to national defense. Dr. Ebbs gave a report similar to that given today, and the members of the conference were so impressed that a resolution was drawn up to provide for further work to be done along these lines.

Subacute Necrosis of the Liver and Peptic Ulcer of the Duodenum. Dr. Roy Simpson, Toronto.

A 17 month old girl was admitted to the hospital because of vomiting. There was a history of difficulty in feeding from birth. Within forty-eight hours of the onset of the present attack of vomiting the patient began to have hematemesis and to pass dark tarry stools. These symptoms continued. There was also some enlargement of the liver. Thirteen days after admission laparotomy was performed to ascertain the source of the hemorrhage from the gastrointestinal tract. Biopsy of the liver revealed subacute necrosis. The child's condition became rapidly worse, and she died fifteen days after admission.

At autopsy the liver was a mottled yellowish brown and slightly shrunken. There was fine wrinkling of the capsule. The small and large intestines contained much altered blood. The sources of this hemorrhage were two ulcers of the proximal portion of the duodenum. In addition, the kidneys showed marked fatty changes, and there was bilateral bronchopneumonia.

DISCUSSION

DR. G. A. CAMPBELL, Ottawa, Ontario: I should like to ask whether the spleen was normal.

DR. ROY SIMPSON, Toronto: Yes.

A Case of Malignant Thymoma. DR. G. A. CAMPBELL, Ottawa, Ontario.

The case of a 22 month old child with lymphosarcoma of the thymus (so-called malignant thymoma) is reported. The thymic tumor was extremely radiosensitive. Metastases occurred within the orbit a few weeks after the growth was discovered in the thymus. The metastases were treated surgically and with radium, but probably not adequately, and further metastases were later noted in the spleen and liver. A fatal issue occurred three months after the appearance of the major symptoms.

Malignant thymoma is a rapidly progressive tumor which metastasizes rapidly, and unless all metastases are discovered early and treated thoroughly with high voltage roentgen therapy and radium a rapidly fatal outcome may be expected.

DISCUSSION

DR. EDWARD MORGAN, Toronto: Was there a leukemic blood picture?

DR. G. A. CAMPBELL, Ottawa, Ontario: Yes. The white blood cell count was high, but no differential count was made.

Book Reviews

Abdominal Surgery of Infancy and Childhood. By William E. Ladd, M.D., and Robert E. Gross, M.D. Price, $10. Pp. 455, with 268 illustrations and 39 tables. Philadelphia: W. B. Saunders Company, 1941.

This book clearly demonstrates how well the surgeon has cooperated with the pediatrician in explaining and treating the numerous abdominal conditions encountered in children. The authors state in their preface, "Our aim is to set forth personal observations and practices so that they will be available to the obstetrician, pediatrician, general practitioner and general surgeon who must diagnose and treat abdominal conditions in infancy and childhood." Because they have had a large experience in the field of pediatric surgery, the authors are well qualified to speak as authoritatively as they do on this subject.

A knowledge of embryology is essential to an understanding of many of the strange conditions which may cause abdominal trouble at any age in childhood. In discussions of the many subjects in this book in which such knowledge is important the embryonic factors have been clearly set forth and comment made on their relation to the pathologic condition. Careful pathologic descriptions, which are equally important, are included. Not only the anatomic features but the pathogenesis of the various conditions are thoroughly discussed.

In every chapter the symptoms and the manner of arriving at the diagnosis of the ailment are so definitely outlined and the differential conditions which should be considered are so clearly indicated that the reader should be enabled to avoid errors in recognition in large measure.

The average reader of most medical books is prone to be very critical, and perhaps rightly so, of the indecisive treatment suggested for various conditions. This treatise can bring forth no such criticism, for the authors advise without equivocation the modes of treatment which they have found most effective, and they give statistics to support their advice. Although one may question the wisdom of some of their suggestions, it must be remembered that their advice is founded on a large experience and deserves thoughtful consideration.

This book is probably not to be regarded as a complete exposition of abdominal surgery in children, for such important subjects as femoral hernia, tuberculous peritonitis and abdominal injuries have been omitted. Retroperitoneal tumors, with the exception of Wilms tumors and neuroblastomas, are not discussed. Extrophy of the bladder is well treated, but other conditions of the kidney and the urinary tract are not taken up. It is to be hoped that the authors will cover these subjects in a future edition.

It has been a pleasure to review this book, which contains so much good, sensible surgical teaching and so little material, if any, to criticize. The text is clear and readable and is made more valuable by a profusion of excellent illustrations. This is a beautiful volume, which is small enough to be handled easily and is a credit to the printing craft. It is recommended without reservation to all who are interested in abdominal conditions in children.

Lymphatics, Lymph and Lymphoid Tissue—Their Physiological and Clinical Significance. Harvard University Monograph in Medicine and Public Health, No. 2. By Cecil Kent Drinker and Joseph Mendel Yoffey. Price, $4.00. Pp. 406, with 50 illustrations. Cambridge, Mass.: Harvard University Press, 1941.

About eight years ago Drinker served as co-author of a monograph on the lymphatics. This is not a revision of that text. The present volume is a current and comprehensive presentation of the physiologic and clinical significance of the

lymphatic system. The chapters on lymphoid tissue were written by the junior author, Yoffey, and the section on electrolytes by A. Baird Hastings. In organization the book is both scholarly and practical, and it should serve as an authoritative source of information on the scientific and practical significance of the anatomic and physiologic aspects of the lymphatic system. The monograph is thoroughly documented; about 43 pages are devoted to the bibliography, and numerous tables and adequate illustrations are also included.

The discussion of the anatomic and physiologic aspects of the lymphatic system is concise but thorough. The permeability of the capillaries and its relation to lymph formation are described and the permeability of the lymphatics, lymph flow and lymph pressure and the chemical and physical characteristics of lymph discussed. The results of a vast amount of experimental work are set forth lucidly and succinctly, and the pertinent literature is judiciously summarized. The chapter entitled "The Biological Significance of the Lymphoid Tissue" is both provocative and practical and contains a large amount of data not ordinarily available to the physician. The functions of the lymphoid tissue in health and in disease are clearly set forth. The chapter on the lymphocyte is exhaustive and complete. The last chapter of the monograph is devoted to practical considerations directly related to the lymph and the lymph vessels.

The monograph will be of special interest to physicians concerned with the basic sciences, but clinicians will find it replete with information which should prove useful in the practice of medicine as well as serving as a basis for creative thinking.

Essentials of Electrocardiography. By Richard Ashman, Ph.D., and Edgar Hull, M.D. Second edition. Price, $5. Pp. 373, with 122 illustrations. New York: The Macmillan Company, 1941.

The recent edition follows the same general outline that was used in the 1937 edition, but there is considerable amplification of the text. Many of the chapters have been entirely rewritten and contain much new material. A number of excellent illustrations have been added. In the earlier edition a single chapter dealt with the physical and physiologic basis of the electrocardiogram, while in the new edition two chapters are given over to this discussion. The text of these chapters has been altered in many particulars, and some of the newer concepts and theories are now included. Chest leads were given meager attention in the earlier edition, but this edition gives almost a chapter to this subject. One wishes, however, that more of the illustrated curves included chest leads. The description of the changes produced by myocardial infarction has been amplified, and illustrations with chest leads have been added. The electrocardiographic changes produced by digitalis are also discussed in more detail and are well illustrated. The differences between the electrocardiograms of children and those of adults are only briefly touched on under the various headings.

The appendix includes an interesting table showing the differences in the normal duration of the PR interval in adults and in children at the various heart rates. It is to be regretted that the author did not give a more detailed discussion of the characteristics of the electrocardiogram in children. Many recent references have been added to the excellent bibliography. The book is a good text for the general practitioner, and the addition of the new material increases its value as a reference book for teaching.

The Art and Science of Nutrition. By E. E. Hawley and Grace Carden. Price $3.50. Pp. 619, with 139 illustrations and 67 tables. St. Louis: C. V. Mosby & Company, 1941.

This book by Hawley and Carden is in some respects a departure from the conventional text on nutrition. It provides an excellent discussion of foods and their physiology, as well as complete tables of the composition of foods. In

addition, it includes a brief synopsis of many of the diseases for which particular diets are described and many practical suggestions about cooking foods and serving them attractively. This last feature is particularly commendable and timely.

If the book is to be criticized at all, it would be on the ground that the floral arrangements and doilies illustrated do not invariably coincide with the taste of the reviewer. The book is unduly heavy for its size, because of the many colored plates. Although many of the illustrations are appropriate, the reviewer feels that others add relatively little. Most persons become familiar with the external aspect of a ripe banana before they attain the elevated position of a student of dietetics. The full page color plate devoted to the portrayal of a syringe lying on a table surrounded by insulin bottles would also seem to be material suitable for an age group only slightly beyond the kindergarten. These, however, are minor faults. The book on the whole is excellent. It will be a valuable addition to the library of any dietitian, and contains valuable reference material for the physician.

Handbook of Communicable Diseases. By Dr. Franklin H. Top. Price, $7.50. Pp. 682, with 73 illustrations. St. Louis: C. V. Mosby Company, 1941.

The author has arranged the diseases according to the particular portal of entry and method of spread. A consideration of the various disease entities is preceded by a section on immunity, epidemiology, control of communicable diseases and nursing and hospital management of the patient. Dr. Top goes further than most authors of books on communicable diseases and considers such conditions as trichinosis, food poisoning, dysentery, tularemia, hookworm disease, pediculosis and malaria. He has an easy style. The subject matter is clear. The illustrations are excellent, and most of them are in color. The textbook can be used by nurses, medical students and practitioners. The charts and appendix represent a monumental bit of work and are very informative. The glossary is an addition which both physicians and nurses will appreciate.

Infantile Paralysis: A Symposium Delivered at Vanderbilt University, April 1941. Price, $1.25. Pp. 239, with 47 illustrations. New York: The National Foundation for Infantile Paralysis, Inc., 1941.

A symposium on infantile paralysis was delivered in April 1941 at Vanderbilt University under the auspices of the National Foundation for Infantile Paralysis, Inc. There were six lectures. These were collected and bound in book form, making a volume of 239 pages with 575 references and an excellent cross index. The history, etiology, immunology and serology, pathology and pathogenesis, epidemiology and treatment are considered, including the latest available information on each subject. Some of the lectures are particularly distinctive, both for the information and for the excellent English. It is unfortunate, however, that clinical evidence as to pathogenesis and diagnosis is omitted.

Sulfanilamide and Related Compounds in General Practice. By Wesley W. Spink, M.D. Price, $3. Pp. 256, with 12 figures and 4 tables. Chicago: The Year Book Publishers, Inc., 1941.

The book begins with a historical review of therapy with sulfanilamide and its derivatives, and, after a discussion of general principles of treatment, individual drugs and infections are dealt with in the conventional manner. Chapters are also devoted to the use of sulfanilamide and its derivatives in surgery, dermatology and dentistry and in prophylaxis. The reviewer finds himself frequently in disagreement with the author, probably because the author's experience seems to have been confined to adults. This book, like others already published, should be of value chiefly as a handy reference to the early literature and historical developments.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region I. Place: Bellevue-Stratford Hotel, Philadelphia. Time: April 1-3, 1942.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Place: Ambassador Hotel, Los Angeles. Time: April 23-25, 1942.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

American Pediatric Society

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 30-May 2, 1942.

Canadian Society for the Study of Diseases of Children

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Brockville, Ontario. Time: June 14, 1941.

Society for Pediatric Research

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385-24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Vancouver, B. C. Time: June 21, 1941.

Rocky Mountain Pediatric Society

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

Alabama Pediatric Society

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.
Place: Springfield. Time: May 19-21, 1942.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Dr. Edith M. Lincoln, 660 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Jay, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

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